EXHIBIT 1

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON
NEW YORK
SAN FRANCISCO
LONDON
BRUSSELS

PETER O. SAFIR
TEL 202.662.5162
FAX 202.778.5162
PSAFIR@COV.COM

June 10, 2005

BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Rm. 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Docket Number 2005P-0127

Dear Madam or Sir:

The undersigned, on behalf of Aventis Pharmaceuticals Inc. ("Aventis"), a member of the sanofi-aventis Group, submits this reply to the comments of Kali Laboratories, Inc. (Kali) and Olsson, Frank and Weeda, P.C. (Olsson) on Sanofi's March 31, 2005 citizen petition (Docket Number 2005P-0127). That petition requested that if an ANDA applicant is not seeking approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® (leflunomide) 100 mg tablets, that FDA require the applicant to perform *in vivo* bioequivalence testing to confirm that five of its 20 mg tablets are bioequivalent to one Arava® 100 mg tablet.

As an initial matter, we must respond to Olsson's unfounded allegation that we have failed to disclose relevant unfavorable information to the Agency. The allegation is false. First, contrary to Olsson's assertions otherwise, the 100 mg Arava tablet has remained continuously available since the date of approval. ("How Supplied" section of the Arava labeling entries in 2000 through 2005 editions of the PDR, Attachment A). The document produced by Olsson was simply a notice to the trade that the 100 mg tablet was no longer available through pharmacists. That the 100 mg tablet is no longer sold in a trade pack -- but is instead made available to physicians as a sample initiation dose -- is simply irrelevant for purposes of our petition.

2005P-0127

RC 1

Second, Olsson's comment is premised entirely on misinformation: "information in the public domain showing that Aventis discontinued 100 mg Arava tablets over three years ago." (Olsson comment at 2). Aventis has never discontinued the 100 mg Arava tablet. Rather, in January 2002, Aventis discontinued the 100 mg trade package. (Attachment B). Although Aventis stopped selling the 100 mg tablet, it did not stop manufacturing or marketing the 100 mg tablet. Since January 2002, Aventis has made the 100 mg tablet available as a "Physician Starter Sample." The company's www.arava.com website contains a link where doctors can request initiation doses of Arava. (Attachment C). Since 2002, Aventis has distributed more than 200,000 100mg Starter Packs for use by new patients.

That Olsson's client received a letter from the Office of Generic Drugs stating that the "100 mg strength has been discontinued from the market" does not mean that Aventis in fact discontinued the 100 mg Arava tablet. Aventis made no submission to the Agency to withdraw the product. To the contrary, Aventis has paid the drug product fee for the 100 mg tablet each year since the discontinuation of the trade pack. (Attachment D). It appears that FDA had briefly and mistakenly concluded that the product was withdrawn based upon Aventis's "Dear Pharmaceutical Buyer" letter. Aventis became aware of this mistake when the 100 mg tablet was moved to the discontinued products section of the 2004 edition of the Orange Book. (Attachment E). Afterwards, Aventis contacted the Agency and explained that the product was still available as a starter sample for physicians. (Attachment F). In response, FDA confirmed that such sampling falls within the ambit of marketing and advised Aventis to write the Orange Book staff to request that the 100 mg tablet be placed back on the approved drug products list. (*Id.*). The mistake was thus corrected in Cumulative Supplement 7 of the 2004 Orange Book. (Attachment G). The 100 mg tablet is currently and properly listed as a reference listed drug. (Attachment H). The Orange Book accurately reflects that Arava 100 mg tablets are available both for use as a loading dose and for purposes of bioequivalence testing. Because the 2005 Orange Book is available on FDA's website it is surprising that Olsson neglected to mention this in its comment.

FDA previously determined that bioequivalence data are a prerequisite to approval of five of 20 mg tablets as a substitute for the 100 mg loading dose. Without data establishing that five of their 20 mg tablets are bioequivalent to one 100 mg Arava tablet, the ANDAs cannot bear instructions to permit the use of five 20 mg tablets as an alternative to the Arava 100 mg tablet loading dose. Because the ANDA applicants do not have such data, the issue ultimately becomes whether they can carve out the loading dose that was a prerequisite to Arava approval. This question must be answered negatively.

Kali's argument that ANDA applicants need not seek approval of all dosage strengths of the reference product misses the point. Aventis does not contend that ANDA applicants must seek approval of a 100 mg leflunomide tablet. Rather, if a generic applicant does not seek approval of a 100 mg tablet, Aventis maintains that the

applicant must establish that five of its 20 mg tablets are bioequivalent to one 100 mg Arava tablet.[1] Otherwise, it may not label its product so as to permit the use of five 20 mg tablets as an alternative loading dose. The label would thus have to either omit the loading dose or reference a 100 mg tablet that the generic does not manufacture. Neither option should be permitted.

As set forth more fully in the original petition, omission of the loading dose would render the proposed generics not safe and effective. The loading dose is not the type of information that can be omitted from an ANDA label simply because the drug is manufactured by a different entity than the reference listed drug. 21 CFR § 314.94(a)(7), (a)(8)(iv); *see also* Draft Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications (Oct. 2000). Thus, if the applicants do not intend to seek approval of a 100 mg tablet, FDA should require them to establish that 5 of their 20 mg tablets are bioequivalent to the 100 mg Arava tablet so that they may include this alternative loading dose regime. Without such a showing the ANDAs cannot be properly labeled.

The oxycodone hydrochloride extended-release tablets example Kali cites is inapposite. There, Teva obtained approval of only an 80 mg tablet. The reference drug, Oxycontin® (oxycodone HCl controlled-release) is available in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablets. Like the labeling of the reference drug Oxycontin, Teva's ANDA includes a statement that "[d]ose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC)." Here, in contrast, dose proportionality has not been established between the various dosage strengths. Indeed, FDA has itself said that bioequivalence data would be required in order for five 20 mg Arava tablets to be used interchangeably with a single 100 mg tablet. Without such data, then there is no basis for any ANDA holder with approval of only a 20 mg leflunomide tablet to include the requisite labeling for the 100 mg loading dose. Such an ANDA should not be approved.

****

[1] To avoid the type of "Catch-22" situation Kali claims would arise if FDA required bioequivalence testing to the 100 mg tablet, Kali may seek sufficient 100 mg tablets for testing from Aventis.

Aventis appreciates this opportunity to respond to Kali's and Olsson's comments.

Respectfully submitted,

Peter O. Safir
Kelly A. Falconer
1201 Pennsylvania Avenue, NW
Washington, DC 20004
(202) 662-5000

Counsel for Aventis

PDR®

54

EDITION

2000

PHYSICIANS' DESK REFERENCE®

Senior Vice President, Directory Services: Paul Walsh

Director of Product Management: Mark A. Friedman
Associate Product Manager: Bill Shaughnessy
Senior Business Manager: Mark S. Ritchin
Financial Analyst: Wayne M. Soltis
Director of Sales: Dikran N. Barsamian
National Sales Manager, Pharmaceutical Sales: Anthony Sorce
National Account Manager: Don Bruccoleri
Senior Account Manager: Frank Karkowsky
Account Managers:
Marion Gray, RPh
Lawrence C. Keary
Jeffrey F. Pfohl
Suzanne E. Yarrow, RN
Electronic Sales Account Manager: Stephen M. Silverberg
National Sales Manager, Medical Economics Trade Sales: Bill Gaffney
Director of Direct Marketing: Michael Bennett
List and Production Manager: Lorraine M. Loening
Senior Marketing Analyst: Dina A. Maeder

Director, New Business Development and Professional Support Services: Mukesh Mehta, RPh
Manager, Drug Information Services: Thomas Fleming, RPh
Drug Information Specialist: Maria Deutsch, MS, RPh, CDE
Editor, Directory Services: David W. Sifton
Senior Associate Editor: Lori Murray
Director of Production: Carrie Williams
Manager of Production: Kimberly H. Vivas
Senior Production Coordinator: Amy B. Brooks
Production Coordinators: Gianna Caradonna, Maria Volpati
Data Manager: Jeffrey D. Schaefer
Senior Format Editor: Gregory J. Westley
Index Editors: Johanna M. Mazur, Robert N. Woerner
Art Associate: Joan K. Akerlind
Senior Digital Imaging Coordinator: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Electronic Publishing Designer: Livio Udina
Fulfillment Manager: Stephanie DeNardi

Officers of Medical Economics Company: *President and Chief Executive Officer:* Curtis B. Allen; *Vice President, New Media:* L. Suzanne BeDell; *Vice President, Corporate Human Resources:* Pamela M. Bilash; *Vice President and Chief Information Officer:* Steven M. Bressler; *Chief Financial Officer:* Christopher Caridi; *Vice President and Controller:* Barry Gray; *Vice President, New Business Planning:* Linda G. Hope; *Vice President, Business Integration:* David A. Pitler; *Vice President, Finance:* Donna Santarpia; *Senior Vice President, Directory Services:* Paul Walsh; *Senior Vice President, Operations:* John R. Ware; *Senior Vice President, Internet Strategies:* Raymond Zoeller

Hemic and Lymphatic System: n. , (including iron deficiency anemia), ecchymosis
Metabolic and Nutritional: creatine phosphokinase increased, peripheral edema, hyperglycemia, hyperlipidemia
Musculoskeletal System: arthrosis, bursitis, muscle cramps, myalgia, bone necrosis, bone pain, tendon rupture
Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweat, vertigo
Respiratory System: asthma, dyspnea, epistaxis, lung disorder
Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, nail disorder, skin nodule, subcutaneous nodule, maculopapular rash, skin disorder, skin discoloration, ulcer skin
Special Senses: blurred vision, cataract, conjunctivitis, eye disorder, taste perversion
Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, vaginal moniliasis, prostate disorder, urinary frequency
Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occurred in Phase II following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000 G/L (rare). A causal relationship of these events to leflunomide has not been established.

DRUG ABUSE AND DEPENDENCE

ARAVA has no known potential for abuse or dependence.

OVERDOSAGE

There is no human experience regarding leflunomide overdosage. In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200 to 500 mg/kg and 100 mg/kg, respectively (approximately >350 times the maximum recommended human dose, respectively).
In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination. Cholestyramine given orally at a dose of 8 g 3 times a day for 24 hours to 3 healthy volunteers decreased plasma levels of M1 by approximately 40% in 24 hours and by 49% to 65% in 48 hours.
Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite, M1, by 37% in 24 hours and by 48% in 48 hours.
These drug elimination procedures may be repeated if clinically necessary.

DOSAGE AND ADMINISTRATION

Loading Dose
Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100-mg tablet per day for 3 days.
Maintenance Therapy
Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n=104) treated with 25 mg/day experienced a greater incidence of side effects: alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes should be monitored and dose adjustments may be necessary (see WARNINGS: *Hepatotoxicity*). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA tablets in 10- and 20-mg strengths are packaged in bottles. ARAVA tablets 100-mg strength are packaged in blister packs.
[See second table on previous page]
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.
Rx only.

Prescribing Information as of September 1998A

Manufactured by
Usiphar, 60200 Compiegne, France
for
Hoechst Marion Roussel, Inc.
Kansas City, MO 64137
Made in France

Shown in Product Identification Guide, page 317

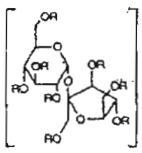
CARAFATE® Tablets

(kăr 'ə făt')
(sucralfate)

Prescribing information as of May 1996

DESCRIPTION

CARAFATE Tablets contain sucralfate and sucralfate is an α-D-glucopyranoside, β-D-fructofuranosyl-, octakis-(hydrogen sulfate), aluminum complex.
[See chemical structure at top of next column]
Tablets for oral administration contain 1 g of sucralfate.
Also contain: D&C Red #30 Lake, FD&C Blue #1 Lake, magnesium stearate, microcrystalline cellulose, and starch.
Therapeutic category: antiulcer.



$[Al(OH)_3]_x[H_2O]_y$
$(x = 8 \text{ to } 10 \text{ and } y = 22 \text{ to } 31)$

$R = SO_3Al(OH)_2$

CLINICAL PHARMACOLOGY

Sucralfate is only minimally absorbed from the gastrointestinal tract. The small amounts of the sulfated disaccharide that are absorbed are excreted primarily in the urine.
Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic, action. The following observations also appear pertinent:
1. Studies in human subjects and with animal models of ulcer disease have shown that sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site.
2. In vitro, a sucralfate-albumin film provides a barrier to diffusion of hydrogen ions.
3. In human subjects, sucralfate given in doses recommended for ulcer therapy inhibits pepsin activity in gastric juice by 32%.
4. In vitro, sucralfate adsorbs bile salts.

These observations suggest that sucralfate's antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14 to 16 mEq of acid-neutralizing capacity per 1-g dose of sucralfate.

CLINICAL TRIALS

Acute Duodenal Ulcer
Over 600 patients have participated in well-controlled clinical trials worldwide. Multicenter trials conducted in the United States, both of them placebo-controlled studies with endoscopic evaluation at 2 and 4 weeks, showed:

STUDY 1

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	37/105 (35.2%)	82/109 (75.2%)
Placebo	28/106 (24.5%)	68/107 (63.6%)

STUDY 2

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	8/24 (33%)	22/24 (92%)
Placebo	4/31 (13%)	18/31 (58%)

The sucralfate-placebo differences were statistically significant in both studies at 4 weeks but not at 2 weeks. The poorer result in the first study may have occurred because sucralfate was given 2 hours after meals and at bedtime rather than 1 hour before meals and at bedtime, the regimen used in international studies and in the second United States study. In addition, in the first study liquid antacid was utilized as needed, whereas in the second study antacid tablets were used.
Maintenance Therapy After Healing of Duodenal Ulcer
Two double-blind randomized placebo-controlled U.S. multicenter trials have demonstrated that sucralfate (1 g bid) is effective as maintenance therapy following healing of duodenal ulcers.
In one study, endoscopies were performed monthly for 4 months. Of the 254 patients who enrolled, 239 were analyzed in the intention-to-treat life table analysis presented below.

Duodenal Ulcer Recurrence Rate (%)

Drug	Months of Therapy				
	n	1	2	3	4
CARAFATE	122	20*	30*	38†	42†
Placebo	117	33	46	55	63

*P<0.05, †P<0.01

In this study, prn antacids were not permitted.
In the other study, scheduled endoscopies were performed at 6 and 12 months, but for-cause endoscopies were permitted as symptoms dictated. Median symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention-to-treat analysis for the 94 patients enrolled in the trial had the following results:

Duodenal Ulcer Recurrence Rate (%)

Drug	n	6 months	12 months
CARAFATE	48	19*	27*
Placebo	46	54	65

*P<0.002

In this study, prn antacids were permitted.
Data from placebo-controlled studies longer than 1 year are not available.

INDICATIONS AND USAGE

CARAFATE® (sucralfate) is indicated in:
- Short-term treatment (up to 8 weeks) of active duodenal ulcer. While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the posthealing frequency or severity of duodenal ulceration.
Special Populations: Chronic Renal Failure and Dialysis Patients
When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum, such as aluminum-containing antacids, may increase the total body burden of aluminum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum-containing products adequately excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin plasma proteins. Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure.
Drug Interactions
Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses of the following: cimetidine, digoxin, fluoroquinolone antibiotics, ketoconazole, l-thyroxine, phenytoin, quinidine, ranitidine, tetracycline, and theophylline. Subtherapeutic prothrombin times with concomitant warfarin and sucralfate therapy have been reported in spontaneous and published case reports. However, two clinical studies have demonstrated no change in either serum warfarin concentration or prothrombin time with the addition of sucralfate to chronic warfarin therapy.
The mechanism of these interactions appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. In all cases studied to date (cimetidine, ciprofloxacin, digoxin, norfloxacin, ofloxacin, and ranitidine), dosing the concomitant medication 2 hours before sucralfate eliminated the interaction. Because of the potential of CARAFATE to alter the absorption of some drugs, CARAFATE should be administered separately from other drugs when alterations in bioavailability are felt to be critical. In these cases, patients should be monitored appropriately.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 g/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.
Pregnancy
Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2700 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Continued on next page

PDR®

55 EDITION

2001

PHYSICIANS' DESK REFERENCE®

Senior Vice President, Directory Services: Paul Walsh

Vice President, Sales and Marketing: Dikran N. Barsamian
National Sales Manager, Custom Sales: Anthony Sorce
Senior Account Manager: Frank Karkowsky
Account Managers:
Marion Gray, RPh
Lawrence C. Keary
Suzanne E. Yarrow, RN
National Sales Manager, Medical Economics Trade Sales:
Bill Gaffney
Senior Business Manager: Mark S. Ritchin
Financial Analyst: Wayne M. Soltis
Vice President, Clinical Communications and New Business Development: Mukesh Mehta, RPh
New Business Development Manager: Jeffrey D. Dubin
Manager, Drug Information Services: Thomas Fleming, RPh
Drug Information Specialists: Maria Deutsch, MS, PharmD, CDE; Christine Wyble, PharmD
Editor, Directory Services: David W. Sifton
Project Manager: Edward P. Connor

Senior Associate Editor: Lori Murray
Assistant Editor: Gwynned L. Kelly
Director of Direct Marketing: Michael Bennett
Direct Mail Manager: Lorraine M. Loening
Senior Marketing Analyst: Dina A. Maeder
Director of Production: Carrie Williams
Data Manager: Jeffrey D. Schaefer
Production Manager: Amy Brooks
Production Coordinators: Gianna Caradonna, Dee Ann DeRuvo, Melissa Katz
Index Supervisor: Johanna M. Mazur
Index Editor: Shannon Reilly
Art Associate: Joan K. Akerlind
Digital Imaging Supervisor: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Pharmaceutical Coordinator: Mary Kaadan
Electronic Publishing Designer: Livio Udina
Fulfillment Managers: Louis J. Bolcik, Stephanie DeNardi

MEDICAL ECONOMICS
THOMSON HEALTHCARE

Officers of Medical Economics Company: *President and Chief Executive Officer:* Curtis B. Allen; *Vice President, New Media:* L. Suzanne BeDell; *Vice President, Corporate Human Resources:* Pamela M. Bilash; *Chief Financial Officer:* Christopher Cardi; *Vice President and Controller:* Barry Gray; *Vice President, Finance:* Donna Santarpia; *Senior Vice President, Directory Services:* Paul Walsh; *Senior Vice President, Operations:* John R. Ware

ISBN: 1-56363-330-2

ARAVA™ (leflunomide) Tablets

Strength	Quantity	NDC Number	Description
10 mg	30 count bottle 100 count bottle	0088-2160-30 0088-2160-47	White, round film-coated tablet embossed with "ZBN" on one side.
20 mg	30 count bottle 100 count bottle	0088-2161-30 0088-2161-47	Light yellow, triangular film-coated tablet embossed with "ZBO" on one side.
100 mg	3 count blister pack	0088-2162-03	White, round film-coated tablet embossed with "ZBP" on one side.

NSAIDs
In *in vitro* studies, M1 was shown to cause increases ranging from 13–50% in the free fraction of diclofenac and ibuprofen at concentrations in the clinical range. The clinical significance of this finding is unknown, however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Tolbutamide
In *in vitro* studies, M1 was shown to cause increases ranging from 13–50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown.

Rifampin
Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both ARAVA and rifampin.

Pediatric Use
The safety and efficacy of ARAVA in the pediatric population have not been studied. Use of ARAVA in patients less than 16 years of age is not recommended.

Geriatric Use
No dosage adjustment is needed in patients over 65.

ADVERSE REACTIONS

Adverse reactions associated with the use of leflunomide in RA include diarrhea, elevated liver enzymes (ALT and AST), alopecia and rash. In the controlled studies, the following adverse events were reported, regardless of causality. (See Table 5.)

[See table 6 at top of previous page]

In addition, the following adverse events have been reported in 1% to <3% of the RA patients in the leflunomide treatment group in controlled clinical trials.

Body as a Whole: abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain;

Cardiovascular: angina pectoris, migraine, palpitation, tachycardia, varicose vein, vasculitis, vasodilatation;

Gastrointestinal: cholelithiasis, colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder;

Endocrine: diabetes mellitus, hyperthyroidism;

Hemic and Lymphatic System: anemia (including iron deficiency anemia), ecchymosis;

Metabolic and Nutritional: creatinine phosphokinase increased, hyperglycemia, hyperlipidemia, peripheral edema;

Musculo-Skeletal System: arthrosis, bone necrosis, bone pain, bursitis, muscle cramps, myalgia, tendon rupture;

Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating increased, vertigo;

Respiratory System: asthma, dyspnea, epistaxis, lung disorder;

Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, maculopapular rash, nail disorder, skin discoloration, skin disorder, skin nodule, subcutaneous nodule, ulcer skin;

Special Senses: blurred vision, cataract, conjunctivitis, eye disorder, taste perversion.

Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, prostate disorder, urinary frequency, vaginal moniliasis.

Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occurred in Phase 2 following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000 WBC/mm^3 (rare). In postmarketing experience, rare cases of pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported.

DRUG ABUSE AND DEPENDENCE

ARAVA has no known potential for abuse or dependence.

OVERDOSAGE

There is no human experience regarding leflunomide overdosage. In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200–500 mg/kg and 100 mg/kg, respectively (approximately >350 times the maximum recommended human dose, respectively).

In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination (see PRECAUTIONS—General—Need for Drug Elimination).

DOSAGE AND ADMINISTRATION

Loading Dose
Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.

Maintenance Therapy
Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n = 104), treated with 25 mg/day, experienced a greater incidence of side effects; alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes should be monitored and dose adjustments may be necessary (see WARNINGS—Hepatotoxicity). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA Tablets in 10 and 20 mg strengths are packaged in bottles. ARAVA Tablets 100 mg strength are packaged in blister packs.

[See table above]

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only.

Prescribing Information as of February 2000

Manufactured by
Upsharr, 60200 Compiegne, France
for
Aventis Pharmaceuticals Inc.
(formerly Hoechst Marion Roussel, Inc.)
Kansas City, MO 64137
Made in France

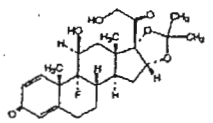
Shown in Product Identification Guide, page 306

AZMACORT® Ⓡ
(*az'ma-kort*)
(triamcinolone acetonide)
Inhalation Aerosol

Rx only
For Oral Inhalation Only
Shake Well Before Using

DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in Azmacort® Inhalation Aerosol, is a corticosteroid with a molecular weight of 434.5 and with the chemical designation 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. ($C_{24}H_{31}FO_6$).



Azmacort Inhalation Aerosol is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in the propellant dichlorodifluoromethane and dehydrated alcohol USP 1% *w/w*. Each canister contains 60 mg triamcinolone acetonide. The canister must be primed prior to the first use. After initial priming of 2 actuations, each actuation delivers 200 mcg triamcinolone acetonide from the valve and 100 mcg from the spacer-mouthpiece under defined *in vitro* test conditions. The canister will remain primed for 3 days. If the canister is not used for more than 3 days, then it should be reprimed with 2 actuations. There are at least 240 actuations in one Azmacort Inhalation Aerosol canister. After 240 actuations, the amount delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

Triamcinolone acetonide is a more potent derivative of triamcinolone. Although triamcinolone itself is approximately one to two times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is approximately 8 times more potent than prednisone.

The precise mechanism of the action of glucocorticoids in asthma is unknown. However, the inhaled route makes it possible to provide effective local anti-inflammatory activity with reduced systemic corticosteroid effects. Though highly effective for asthma, glucocorticoids do not affect asthma symptoms immediately. While improvement in asthma may occur as soon as one week after initiation of Azmacort Inhalation Aerosol therapy, maximum improvement may not be achieved for 2 weeks or longer.

Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.5 L (SD ± 27.5) and clearance was 45.2 L/hour (SD ± 9.1) for triamcinolone acetonide. The plasma half-life of glucocorticoids does not correlate well with the biologic half-life.

The pharmacokinetics of radiolabeled triamcinolone acetonide [^{14}C] were evaluated following a single oral dose of 800 mcg to healthy male volunteers. Radiolabeled triamcinolone acetonide was found to undergo relatively rapid absorption following oral administration with maximum plasma triamcinolone acetonide and [^{14}C]-derived radioactivity occurring between 1.5 and 2 hours. Plasma protein binding of triamcinolone acetonide appears to be relatively low and consistent over a wide plasma triamcinolone acetonide concentration range as a function of time. The overall mean percent fraction bound was approximately 68%.

The metabolism and excretion of triamcinolone acetonide were both rapid and extensive with no parent compound being detected in the plasma after 24 hours post-dose and a low ratio (10.6%) of parent compound $AUC_{0-\infty}$ to total [^{14}C] radioactivity $AUC_{0-\infty}$. Greater than 90% of the oral [^{14}C]-radioactive dose was recovered within 5 days after administration in 5 out of the 6 subjects in the study. Of the recovered [^{14}C]-radioactivity, approximately 40% and 60% were found in the urine and feces, respectively.

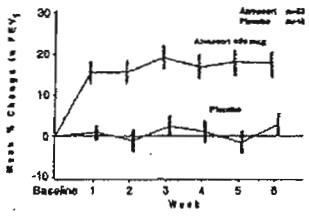
Three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

CLINICAL TRIALS

Double-blind, placebo controlled efficacy and safety studies have been conducted in asthma patients with a range of asthma severities, from those patients with mild disease to those with severe disease requiring oral steroid therapy.

The efficacy and safety of Azmacort Inhalation Aerosol given twice daily was demonstrated in two placebo-controlled clinical trials. In two separate studies, 222 asthmatic patients were randomized to receive either Azmacort Inhalation Aerosol 400 mcg twice daily or matching placebo for a treatment period of 6 weeks. Patients were adult asthmatics who were using inhaled beta$_2$-agonists on more than an occasional basis (at least three times weekly), either without or with inhaled corticosteroids, for control of their asthma symptoms. For the combined studies, 48% (52/109) patients randomized to placebo and 41% (46/113) patients randomized to Azmacort treatment were previously treated with inhaled corticosteroids.

Results of weekly lung function tests (FEV_1) from one of these trials is presented graphically below. Results of the second study are presented in tabular form as the changes in asthma measures from baseline to the end of the treatment period.



Mean Changes in Asthma Measures from Baseline to Endpoint[A]
All-Treated Patients
Results from a Placebo-Controlled, 6 Week Study

Asthma Measure	Placebo (N=61)	Azmacort 400 mcg bid (N=60)
Percent Change in FEV_1(%)	2.8%	17.5%
Increase in Morning Peak Flow Rate (L/min)	6.7	45.9

PHYSICIANS' DESK REFERENCE®

Executive Vice President, Directory Services: Paul Walsh

Vice President, Sales and Marketing: Dikran N. Barsamian
National Sales Manager: John A. Schmidt
National Sales Manager, Custom Sales: Anthony Sorce
Senior Account Managers: Marion Gray, RPh; Frank Karkowsky
Account Managers: Lawrence C. Keary; Eileen Sullivan; Suzanne E. Yarrow, RN
Director of Trade Sales: Bill Gaffney
Associate Product Manager: Jason R. Springer
Director of Financial Planning and Analysis: Mark S. Ritchin
Vice President, Clinical Communications and New Business Development: Mukesh Mehta, RPh
New Business Development Manager: Jeffrey D. Dubin
Manager, Professional Data Services: Thomas Fleming, PharmD
Manager, Concise Data Content: Christine Wyble, PharmD
Drug Information Specialists: Maria Deutsch, MS, PharmD, CDE; Anu Gupta, PharmD
Editor, Directory Services: David W. Sifton
Project Manager: Edward P. Connor

Senior Associate Editor: Lori Murray
Assistant Editor: Gwynned L. Kelly
Director of Direct Marketing: Michael Bennett
Direct Mail Managers: Jennifer M. Fronzaglia, Lorraine M. Loening
Senior Marketing Analyst: Dina A. Maeder
Promotion Manager: Linda Levine
Director of Production: Brian Holland
Senior Data Manager: Jeffrey D. Schaefer
Production Manager: Amy Brooks
Production Coordinators: Gianna Caradonna, DeeAnn DeRuvo, Melissa Johnson, Christina Klinger
Index Editors: Noel Deloughery, Shannon Reilly
Format Editor: Stu W. Lehrer
Art Associate: Joan K. Akerlind
Digital Imaging Supervisor: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Electronic Publishing Designers: Rosalia Sberna, Livio Udina
Fulfillment Managers: Louis J. Bolcik, Stephanie Struble

MEDICAL ECONOMICS
THOMSON HEALTHCARE

Officers of Thomson Healthcare: Chief Executive Officer: Michael Tansey; *Chief Operating Officer:* Richard Noble; *Chief Financial Officer and Executive Vice President, Finance:* Paul Hilger; *Executive Vice President, Directory Services:* Paul Walsh; *Senior Vice President, Planning and Business Development:* William Gole; *Vice President, Human Resources:* Pamela M. Bilash

ISBN: 1-56363-411-2

Arava—Cont.

be considered when leflunomide treatment is followed by such drugs without a drug elimination procedure. In a small (n=30) combination study of ARAVA with methotrexate, a 2- to 3-fold elevation in liver enzymes was seen in 5 of 30 patients. All elevations resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. A >3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. Three patients met "ACR criteria" for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa). No pharmacokinetic interaction was identified (see CLINICAL PHARMACOLOGY).

NSAIDs

In *in vitro* studies, M1 was shown to cause increases ranging from 13–50% in the free fraction of diclofenac and ibuprofen at concentrations in the clinical range. The clinical significance of this finding is unknown, however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Tolbutamide

In *in vitro* studies, M1 was shown to cause increases ranging from 13–50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown.

Rifampin

Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both ARAVA and rifampin.

Pediatric Use

The safety and efficacy of ARAVA in the pediatric population have not been studied. Use of ARAVA in patients less than 18 years of age is not recommended.

Geriatric Use

No dosage adjustment is needed in patients over 65.

ADVERSE REACTIONS

Adverse reactions associated with the use of leflunomide in RA include diarrhea, elevated liver enzymes (ALT and AST), alopecia and rash. In the controlled studies, the following adverse events were reported, regardless of causality. (See Table 5.)

(See table at top of previous page)

In addition, the following adverse events have been reported in 1% to <3% of the RA patients in the leflunomide treatment group in controlled clinical trials.

Body as a Whole: abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain;

Cardiovascular: angina pectoris, migraine, palpitation, tachycardia, varicose vein, vasculitis, vasodilatation;

Gastrointestinal: cholelithiasis, colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder;

Endocrine: diabetes mellitus, hyperthyroidism;

Hemic and Lymphatic System: anemia (including iron deficiency anemia), ecchymosis;

Metabolic and Nutritional: creatinine phosphokinase increased, hyperglycemia, hyperlipidemia, peripheral edema;

Musculo-Skeletal System: arthrosis, bone necrosis, bone pain, bursitis, muscle cramps, myalgia, tendon rupture;

Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating increased, vertigo;

Respiratory System: asthma, dyspnea, epistaxis, lung disorder;

Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, maculopapular rash, nail disorder, skin discoloration, skin disorder, skin nodule, subcutaneous nodule, ulcer skin;

Special Senses: blurred vision, cataract, conjunctivitis, eye disorder, taste perversion.

Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, prostate disorder, urinary frequency, vaginal moniliasis.

Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occurred in Phase 2 following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000 WBC/mm³ (rare). In postmarketing experience, rare cases of pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported.

DRUG ABUSE AND DEPENDENCE

ARAVA has no known potential for abuse or dependence.

OVERDOSAGE

There is no human experience regarding leflunomide overdosage. In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200–500 mg/kg and 100 mg/kg, respectively (approximately >350 times the maximum recommended human dose, respectively).

In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination (see PRECAUTIONS—General—Need for Drug Elimination).

DOSAGE AND ADMINISTRATION

Loading Dose

Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.

Maintenance Therapy

Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n=104), treated with 25 mg/day, experienced a greater incidence of side effects: alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes should be monitored and dose adjustments may be necessary (see WARNINGS—Hepatotoxicity). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA Tablets in 10 and 20 mg strengths are packaged in bottles. ARAVA Tablets 100 mg strength are packaged in blister packs.

(See table below)

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only.

Prescribing Information as of April 2000A

Manufactured by
Upjohn, 60200 Compiegne, France
for
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137
Made in France
50054389

Shown in Product Identification Guide, page 306

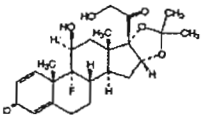
AZMACORT®

[az´ma-kort]
(triamcinolone acetonide)
Inhalation Aerosol

Rx only
For Oral Inhalation Only
Shake Well Before Using
Prescribing Information as of March 1999

DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in Azmacort® Inhalation Aerosol, is a corticosteroid with a molecular weight of 434.5 and with the chemical designation 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. ($C_{24}H_{31}FO_6$).



Azmacort Inhalation Aerosol is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in the propellant dichlorodifluoromethane and dehydrated alcohol USP 1% w/w. Each canister contains 60 mg triamcinolone acetonide. The canister must be primed prior to the first use. After initial priming of 2 actuations, each actuation delivers 200 mcg triamcinolone acetonide from the valve and 100 mcg from the spacer-mouthpiece under defined *in vitro* test conditions. The canister will remain primed for 3 days. If the canister is not used for more than 3 days, then it should be reprimed with 2 actuations. There are at least 240 actuations in one Azmacort Inhalation Aerosol canister. After 240 actuations, the amount delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

Triamcinolone acetonide is a more potent derivative of triamcinolone. Although triamcinolone itself is approximately one to two times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is approximately 8 times more potent than prednisone.

The precise mechanism of the action of glucocorticoids in asthma is unknown. However, the inhaled route makes it possible to provide effective local anti-inflammatory activity with reduced systemic corticosteroid effects. Though highly effective for asthma, glucocorticoids do not affect asthma symptoms immediately. While improvement in asthma may occur as soon as one week after initiation of Azmacort Inhalation Aerosol therapy, maximum improvement may not be achieved for 2 weeks or longer.

Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.5 L (SD ± 27.5) and clearance was 45.2 L/hour (SD ± 9.1) for triamcinolone acetonide. The plasma half-life of glucocorticoids does not correlate well with the biologic half-life.

The pharmacokinetics of radiolabeled triamcinolone acetonide [^{14}C] were evaluated following a single oral dose of 800 mcg to healthy male volunteers. Radiolabeled triamcinolone acetonide was found to undergo relatively rapid absorption following oral administration with maximum plasma triamcinolone acetonide and [^{14}C]-derived radioactivity occurring between 1.5 and 2 hours. Plasma protein binding of triamcinolone acetonide appears to be relatively low and consistent over a wide plasma triamcinolone acetonide concentration range as a function of time. The overall mean percent fraction bound was approximately 68%.

The metabolism and excretion of triamcinolone acetonide were both rapid and extensive with no parent compound being detected in the plasma after 24 hours post-dose and a low ratio (10.6%) of parent compound $AUC_{0-\infty}$ to total [^{14}C] radioactivity $AUC_{0-\infty}$. Greater than 90% of the oral [^{14}C]-radioactive dose was recovered within 5 days after administration in 5 out of the 6 subjects in the study. Of the recovered [^{14}C]-radioactivity, approximately 40% and 60% were found in the urine and feces, respectively.

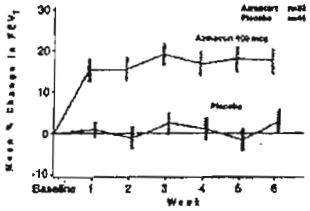
Three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

CLINICAL TRIALS

Double-blind, placebo controlled efficacy and safety studies have been conducted in asthma patients with a range of asthma severities, from those patients with mild disease to those with severe disease requiring oral steroid therapy.

The efficacy and safety of Azmacort Inhalation Aerosol given twice daily was demonstrated in two placebo-controlled clinical trials. In two separate studies, 222 asthmatic patients were randomized to receive either Azmacort Inhalation Aerosol 400 mcg twice daily or matching placebo for a treatment period of 6 weeks. Patients were adult asthmatics who were using inhaled beta$_2$-agonists on more than an occasional basis (at least three times weekly), either without or with inhaled corticosteroids, for control of their asthma symptoms. For the combined studies, 48% (52/109) patients randomized to placebo and 41% (46/113) patients randomized to Azmacort treatment were previously treated with inhaled corticosteroids.

Results of weekly lung function tests (FEV_1) from one of these trials is presented graphically below. Results of the second study are presented in tabular form as the changes in asthma measures from baseline to the end of the treatment period.



ARAVA™ (leflunomide) Tablets

Strength	Quantity	NDC Number	Description
10 mg	30 count bottle 100 count bottle	0088-2160-30 0088-2160-47	White, round film-coated tablet embossed with "ZBN" on one side.
20 mg	30 count bottle 100 count bottle	0088-2161-30 0088-2161-47	Light yellow, triangular film-coated tablet embossed with "ZBO" on one side.
100 mg	3 count blister pack	0088-2162-03	White, round film-coated tablet embossed with "ZBP" on one side.

Information will be summarized here, supplements and subsequent editions

PDR®

57

EDITION

2003

PHYSICIANS' DESK REFERENCE®

Executive Vice President, Directory Services: Paul M. Walsh

Vice President, Sales and Marketing: Dikran N. Barsamian
Director, PDR Pharmaceutical Sales: Anthony Sorce
Senior Account Managers: Frank Karkowsky, Elaine Musco, Marion Reid, RPh
Account Managers: Lawrence C. Keary, Lois Smith, Eileen Sullivan, Suzanne E. Yarrow, RN
Director of Trade Sales: Bill Gaffney
Director of Product Management: Valerie E. Berger
Senior Product Manager: Jeffrey D. Dubin
Finance Director: Mark S. Ritchin
Senior Director, Publishing Sales and Marketing: Michael Bennett
Direct Mail Managers: Jennifer M. Fronzaglia, Lorraine M. Loening
Senior Marketing Analyst: Dina A. Maeder
Promotion Manager: Linda Levine
Vice President, Clinical Communications and Strategic Initiatives: Mukesh Mehta, RPh
Manager, Professional Data Services: Thomas Fleming, RPh
Manager, Concise Data Content: Christine Wyble, PharmD
Drug Information Specialists: Maria Deutsch, MS, PharmD; Anu Gupta, PharmD
Editor, Directory Services: David W. Sifton

Project Manager: Edward P. Connor
Senior Associate Editor: Lori Murray
Associate Editor: Gwynned L. Kelly
Senior Director, Operations: Brian Holland
Senior Data Manager: Jeffrey D. Schaefer
Manager of Production Operations: Thomas Westburgh
Project Manager: Amy B. Brooks
Senior Production Coordinator: Gianna Caradonna
Production Coordinators: DeeAnn DeRuvo, Christina Klinger
Index Supervisor: Joseph F. Rizzo
Index Editors: Noel Deloughery, Shannon Reilly
Format Editor: Kathleen M. Chabalia
Production Associate: Joan K. Akerlind
Production Design Supervisor: Adeline Rich
Electronic Publishing Designers: Bryan Dix, Rosalia Sberna, Livio Udina
Digital Imaging Supervisor: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Director of Client Services: Stephanie Struble
Fulfillment Manager: Louis J. Bolcik

ISBN: 1-56363-445-7

ARAVA™ [leflunomide] Tablet

Strength	Quantity	NDC Number	Description
10 mg	30 count bottle 100 count bottle	0088-2160-30 0088-2160-47	White, round film-coated tablet embossed with "ZBN" on one side.
20 mg	30 count bottle 100 count bottle	0088-2161-30 0088-2161-47	Light yellow, triangular film-coated tablet embossed with "ZBO" on one side.
100 mg	3 count blister pack	0088-2162-03	White, round film-coated tablet embossed with "ZBP" on one side.

resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. Three patients met "ACR criteria" for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa). No pharmacokinetic interaction was identified (see CLINICAL PHARMACOLOGY).

NSAIDs

In vitro studies, M1 was shown to cause increases ranging from 13–60% in the free fraction of diclofenac and ibuprofen at concentrations in the clinical range. The clinical significance of this finding is unknown, however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Tolbutamide

In vitro studies, M1 was shown to cause increases ranging from 13–50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown.

Rifampin

Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both ARAVA and rifampin.

Pediatric Use

The safety and efficacy of ARAVA in the pediatric population have not been studied. Use of ARAVA in patients less than 18 years of age is not recommended.

Geriatric Use

No dosage adjustment is needed in patients over 65.

ADVERSE REACTIONS

Adverse reactions associated with the use of leflunomide in RA include diarrhea, elevated liver enzymes (ALT and AST), alopecia and rash. In the controlled studies, the following adverse events were reported, regardless of causality. (See Table 5.)

[See table at top of previous page]

In addition, the following adverse events have been reported in 1% to <3% of the RA patients in the leflunomide treatment group in controlled clinical trials.

Body as a Whole: abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain;

Cardiovascular: angina pectoris, migraine, palpitation, tachycardia, varicose vein, vasculitis, vasodilatation;

Gastrointestinal: cholelithiasis, colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder;

Endocrine: diabetes mellitus, hyperthyroidism;

Hemic and Lymphatic System: anemia (including iron deficiency anemia), ecchymosis;

Metabolic and Nutritional: creatinine phosphokinase increased, hyperglycemia, hyperlipidemia, peripheral edema;

Musculo-Skeletal System: arthrosis, bone necrosis, bone pain, bursitis, muscle cramps, myalgia, tendon rupture;

Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating increased, vertigo;

Respiratory System: asthma, dyspnea, epistaxis, lung disorder;

Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, maculopapular rash, nail disorder, skin discoloration, skin disorder, skin nodule, subcutaneous nodule, ulcer skin;

Special Senses: blurred vision, cataract, conjunctivitis, eye disorder, taste perversion.

Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, prostate disorder, urinary frequency, vaginal moniliasis.

Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occurred in Phase 2 following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000 WBC/mm^3 (rare). In post-marketing experience, rare cases of pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported.

DRUG ABUSE AND DEPENDENCE

ARAVA has no known potential for abuse or dependence.

OVERDOSAGE

There is no human experience regarding leflunomide overdosage. In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200–600 mg/kg and 100 mg/kg, respectively (approximately >350 times the maximum recommended human dose, respectively).

In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination (see PRECAUTIONS—General—Need for Drug Elimination).

DOSAGE AND ADMINISTRATION

Loading Dose

Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.

Maintenance Therapy

Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n=104), treated with 25 mg/day, experienced a greater incidence of side effects; alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes should be monitored and dose adjustments may be necessary (see WARNINGS—Hepatotoxicity). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA Tablets in 10 and 20 mg strengths are packaged in bottles. ARAVA Tablets 100 mg strength are packaged in blister packs.

[See table above]

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only.

Prescribing Information as of April 2000A

Manufactured by
Upsher, 60200 Compiegne, France
for
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137
Made in France
50054389

Shown in Product Identification Guide, page 306

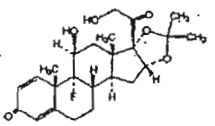
AZMACORT®

[dz 'ma-kort]
(triamcinolone acetonide)
Inhalation Aerosol

Rx only
For Oral Inhalation Only
Shake Well Before Using
Prescribing Information as of February 2001

DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in Azmacort® Inhalation Aerosol, is a corticosteroid with a molecular weight of 434.5 and with the chemical designation 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. ($C_{24}H_{31}FO_6$).



Azmacort Inhalation Aerosol is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in the propellant dichlorodifluoromethane and dehydrated alcohol USP 1% w/w. Each canister contains 60 mg triamcinolone acetonide. The canister must be primed prior to the first use. After an initial priming of 2 actuations, each actuation delivers 200 mcg triamcinolone acetonide from the valve and 100 mcg from the spacer-mouthpiece under defined *in vitro* test conditions. The canister will remain primed for 3 days. If the canister is not used for more than 3 days, then it should be reprimed with 2 actuations. There are at least 240 actuations in one Azmacort Inhalation Aerosol canister. After 240 actuations, the amount delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

Triamcinolone acetonide is a more potent derivative of triamcinolone. Although triamcinolone itself is approximately one to two times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is approximately [illegible] times more potent than prednisone.

The precise mechanism of the action of glucocorticoids in asthma is unknown. However, the inhaled route makes it possible to provide effective local anti-inflammatory activity with reduced systemic corticosteroid effects. Though highly effective for asthma, glucocorticoids do not affect asthma symptoms immediately. While improvement in asthma may occur as soon as one week after initiation of Azmacort Inhalation Aerosol therapy, maximum improvement may not be achieved for 2 weeks or longer.

Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.6 L (SD ± 27.6) and clearance was 45.7 L/hour (SD ± 9.1) for triamcinolone acetonide. The plasma half-life of glucocorticoids does not correlate well with the biologic half-life.

The pharmacokinetics of radiolabeled triamcinolone acetonide [^{14}C] were evaluated following a single oral dose of 800 mcg to healthy male volunteers. Radiolabeled triamcinolone acetonide was found to undergo relatively rapid absorption following oral administration with maximum plasma triamcinolone acetonide and [^{14}C]-derived radioactivity occurring between 1.5 and 2 hours. Plasma protein binding of triamcinolone acetonide appears to be relatively low and consistent over a wide plasma triamcinolone acetonide concentration range as a function of time. The overall mean percent fraction bound was approximately 68%.

The metabolism and excretion of triamcinolone acetonide were both rapid and extensive with no parent compound being detected in the plasma after 24 hours post-dose and a low ratio (10.6%) of parent compound $AUC_{0-\infty}$ to total [^{14}C] radioactivity $AUC_{0-\infty}$. Greater than 90% of the oral [^{14}C] radioactive dose was recovered within 6 days after administration in 5 out of the 6 subjects in the study. Of the recovered [^{14}C]-radioactivity, approximately 40% and 60% were found in the urine and feces, respectively.

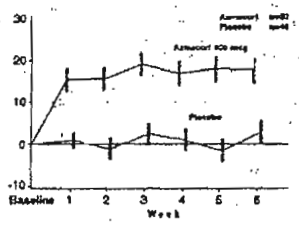
Three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

CLINICAL TRIALS

Double-blind, placebo controlled efficacy and safety studies have been conducted in asthma patients with a range of asthma severities, from those patients with mild disease to those with severe disease requiring oral steroid therapy.

The efficacy and safety of Azmacort Inhalation Aerosol given twice daily was demonstrated in two placebo-controlled clinical trials. In two separate studies, 222 asthmatic patients were randomized to receive either Azmacort Inhalation Aerosol 400 mcg twice daily or matching placebo for a treatment period of 6 weeks. Patients were adult asthmatics who were using inhaled beta$_2$-agonists on more than an occasional basis (at least three times weekly), either without or with inhaled corticosteroids, for control of their asthma symptoms. For the combined studies, 48% (52/109) patients randomized to placebo and 41% (46/113) patients randomized to Azmacort treatment were previously treated with inhaled corticosteroids.

Results of weekly lung function tests (FEV_1) from one of these trials is presented graphically below. Results of the second study are presented in tabular form as the changes in asthma measures from baseline to the end of the treatment period.



Mean Changes in Asthma Measures from Baseline to Endpoint[a]
All-Treated Patients
Results from a Placebo-Controlled, 6 Week Study

Asthma Measure	Placebo (N=61)	Azmacort 400 mcg bid (N=60)
Percent Change in FEV_1 (%)	2.8%	17.5%
Increase in Morning Peak Flow Rate (L/min)	6.7	45.9
Decrease in Albuterol Use (puffs/day)	0.6	3.4

Continued on next page

PDR®

58

EDITION

2004

PHYSICIANS' DESK REFERENCE®

Executive Vice President, Directory Services: David Duplay

Vice President, Sales and Marketing: Dikran N. Barsamian
Senior Director of Pharmaceutical Sales: Anthony Sorce
National Account Manager: Marion Reid, RPh
Senior Account Manager: Frank Karkowsky
Account Managers: Marjorie A. Jaxel, Denise Kelley, Eileen Sullivan, Suzanne E. Yarrow, RN
Director of Trade Sales: Bill Gaffney
Senior Director, Marketing and Product Management: Valerie E. Berger
Senior Product Manager: Jeffrey D. Dubin
Finance Director: Mark S. Ritchin
Senior Director, Publishing Sales and Marketing: Michael Bennett
Senior Marketing Manager: Jennifer M. Fronzaglia
Direct Mail Manager: Lorraine M. Loening
Manager of Marketing Analysis: Dina A. Maeder
Promotion Manager: Linda Levine
Vice President, Regulatory Affairs: Mukesh Mehta, RPh
Editorial Director: Lisette Bralow
Manager, Professional Data Services: Thomas Fleming, PharmD
Manager, Editorial Services: Bette LaGow
Manager, Concise Data Content: Tammy Chemin, RPh

Drug Information Specialists: Greg Tallis, RPh; Min Ko, PharmD
Project Editor: Harris Fleming
Senior Editor: Lori Murray
Production Editor: Gwynned L. Kelly
Senior Director, Operations: Brian Holland
Director of PDR Operations: Jeffrey D. Schaefer
Manager of Production Operations: Thomas Westburgh
PDR Production Manager: Joseph F. Rizzo
Senior Production Coordinators: Gianna Caradonna, Christina Klinger
Production Coordinator: Yasmin Hernández
Senior Index Editor: Shannon Reilly
Index Editor: Noel Deloughery
Format Editor: Michelle S. Guzman
Production Associate: Joan K. Akerlind
Production Design Supervisor: Adeline Rich
Electronic Publishing Designers: Bryan Dix, Rosalia Sberna, Livio Udina
Digital Imaging Coordinator: Michael Labruyere
Director of Client Services: Stephanie Struble
Fulfillment Manager: Louis J. Bolcik

ISBN: 1-56363-471-6

1) Administer cholestyramine 8 g 3 times daily for 11 days. (The 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly.)
2) Verify plasma levels less than 0.2 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered.

Without the drug elimination procedure, it may take up to 2 years to reach plasma M1 metabolite levels less than 0.02 mg/L due to individual variation in drug clearance.

PRECAUTIONS

General

Need for Drug Elimination

The active metabolite of leflunomide is eliminated slowly from the plasma. In instances of any serious toxicity from ARAVA, including hypersensitivity, use of a drug elimination procedure as described in this section is highly recommended to reduce the drug concentration more rapidly after stopping ARAVA therapy. If hypersensitivity is the suspected clinical mechanism, more prolonged cholestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance. The duration may be modified based on the clinical status of the patient.

Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of M1 by approximately 40% in 24 hours and by 49 to 65% in 48 hours.

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite, M1, by 37% in 24 hours and by 48% in 48 hours.

These drug elimination procedures may be repeated if clinically necessary.

Renal Insufficiency

Single dose studies in dialysis patients show a doubling of the free fraction of M1 in plasma. There is no clinical experience in the use of ARAVA in patients with renal impairment. Caution should be used when administering this drug in this population.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations during ARAVA treatment. Vaccination with live vaccines is, however, not recommended. The long half-life of ARAVA should be considered when contemplating administration of a live vaccine after stopping ARAVA.

Information for Patients

The potential for increased risk of birth defects should be discussed with female patients of childbearing potential. It is recommended that physicians advise women that they may be at increased risk of having a child with birth defects if they are pregnant when taking ARAVA, become pregnant while taking ARAVA, or do not wait to become pregnant until they have stopped taking ARAVA and followed the drug elimination procedure (as described in WARNINGS—Use In Women of Childbearing Potential—Drug Elimination Procedure).

Patients should be advised of the possibility of rare, serious skin reactions. Patients should be instructed to inform their physicians promptly if they develop a skin rash or mucous membrane lesions.

Patients should be advised of the potential hepatotoxic effects of ARAVA and of the need for monitoring liver enzymes.

Patients who are receiving other immunosuppressive therapy concurrently with ARAVA, who have recently discontinued such therapy before starting treatment with ARAVA, or who have had a history of significant hematologic abnormality, should be advised of the potential for pancytopenia and of the need for frequent hematologic monitoring. They should be instructed to notify their physicians promptly if they notice symptoms of pancytopenia (such as easy bruising, proneness to infections, paleness or unusual tiredness).

Laboratory tests

At minimum, ALT (SGPT) should be performed at baseline and monitored initially at monthly intervals then, if stable, at intervals determined by the individual clinical situation.

In patients who are at an increased risk of hematologic toxicity (see WARNINGS—Immunosuppression Potential), more vigilant monitoring, including hematologic monitoring, is warranted.

Due to a specific effect on the brush border of the renal proximal tubule, ARAVA has a uricosuric effect. A separate effect of hypophosphaturia is seen in some patients. These effects have not been seen together, nor have there been alterations in renal function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of leflunomide up to the maximally tolerated dose of 6 mg/kg (approximately 1/40 the maximum human M1 systemic exposure based on AUC). However, male mice in a 2-year bioassay exhibited an increased incidence in lymphoma at an oral dose of 15 mg/kg, the highest dose studied (1.7 times the human M1 exposure based on AUC). Female mice, in the same study, exhibited a dose-related increased incidence of bronchoalveolar adenomas and carcinomas combined beginning at 1.5 mg/kg (approximately 1/10 the human M1 exposure based on AUC). The significance of the findings in mice relative to the clinical use of ARAVA is not known.

Leflunomide was not mutagenic in the Ames Assay, the Unscheduled DNA Synthesis Assay, or in the HGPRT Gene Mutation Assay. In addition, leflunomide was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells. However, 4-trifluoromethylaniline (TFMA), a minor metabolite of leflunomide, was mutagenic in the Ames Assay and in the HGPRT Gene Mutation Assay, and was clastogenic in the *in vitro* Assay for Chromosome Aberrations in the Chinese Hamster Cells. TFMA was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells.

Leflunomide had no effect on fertility in either male or female rats at oral doses up to 4.0 mg/kg (approximately 1/30 the human M1 exposure based on AUC).

Pregnancy

Pregnancy Category X. See CONTRAINDICATIONS section. Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to leflunomide, health care providers are encouraged to register such patients by calling 1-877-311-8972.

Nursing Mothers

ARAVA should not be used by nursing mothers. It is not known whether ARAVA is excreted in human milk. Many drugs are excreted in human milk, and there is a potential for serious adverse reactions in nursing infants from ARAVA. Therefore, a decision should be made whether to proceed with nursing or to initiate treatment with ARAVA, taking into account the importance of the drug to the mother.

Use in Males

Available information does not suggest that ARAVA would be associated with an increased risk of male-mediated fetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimize any possible risk, men wishing to father a child should consider discontinuing use of ARAVA and taking cholestyramine 8 grams 3 times daily for 11 days.

Drug Interactions

Cholestyramine and Charcoal

Administration of cholestyramine or activated charcoal in patients (n=13) and volunteers (n=96) resulted in a rapid and significant decrease in plasma M1 (the active metabolite of leflunomide) concentration (see PRECAUTIONS—General—Need for Drug Elimination).

Hepatotoxic Drugs

Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic substances. This is also to be considered when leflunomide treatment is followed by such drugs without a drug elimination procedure. In a small (n=30) combination study of ARAVA with methotrexate, a 2- to 3-fold elevation in liver enzymes was seen in 5 of 30 patients. All elevations resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. A >3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. Three patients met "ACR criteria" for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa). No pharmacokinetic interaction was identified (see CLINICAL PHARMACOLOGY).

NSAIDs

In *in vitro* studies, M1 was shown to cause increases ranging from 13–50% in the free fraction of diclofenac and ibuprofen at concentrations in the clinical range. The clinical significance of this finding is unknown, however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Tolbutamide

In *in vitro* studies, M1 was shown to cause increases ranging from 13–50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown.

Rifampin

Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both ARAVA and rifampin.

Pediatric Use

The safety and efficacy of ARAVA in the pediatric population have not been studied. Use of ARAVA in patients less than 18 years of age is not recommended.

Geriatric Use

No dosage adjustment is needed in patients over 65.

ADVERSE REACTIONS

Adverse reactions associated with the use of leflunomide in RA include diarrhea, elevated liver enzymes (ALT and AST), alopecia and rash. In the controlled studies, the following adverse events were reported, regardless of causality. (See Table 5:)

(See table 5 at top of previous page)

ARAVA™ (leflunomide) Tablets

Strength	Quantity	NDC Number	Description
10 mg	30 count bottle 100 count bottle	0088-2160-30 0088-2160-47	White, round film-coated tablet embossed with "ZBN" on one side.
20 mg	30 count bottle 100 count bottle	0088-2161-30 0088-2161-47	Light yellow, triangular film-coated tablet embossed with "ZBO" on one side.
100 mg	3 count blister pack	0088-2162-03	White, round film-coated tablet embossed with "ZBP" on one side.

In addition, the following adverse events have been reported in 1% to <3% of the RA patients in the leflunomide treatment group in controlled clinical trials.

Body as a Whole: abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain;

Cardiovascular: angina pectoris, migraine, palpitation, tachycardia, varicose vein, vasculitis, vasodilatation;

Gastrointestinal: cholelithiasis, colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder;

Endocrine: diabetes mellitus, hyperthyroidism;

Hemic and Lymphatic System: anemia (including iron deficiency anemia), ecchymosis;

Metabolic and Nutritional: creatinine phosphokinase increased, hyperglycemia, hyperlipidemia, peripheral edema;

Musculo-Skeletal System: arthrosis, bone necrosis, bone pain, bursitis, muscle cramps, myalgia, tendon rupture;

Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating increased, vertigo;

Respiratory System: asthma, dyspnea, epistaxis, lung disorder.

Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, maculopapular rash, nail disorder, skin discoloration, skin disorder, skin nodule, subcutaneous nodule, ulcer skin;

Special Senses: blurred vision, cataract, conjunctivitis, eye disorder, taste perversion.

Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, prostate disorder, urinary frequency, vaginal moniliasis.

Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occurred in Phase 2 following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000 WBC/mm^3 (rare). In postmarketing experience, rare cases of pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported.

DRUG ABUSE AND DEPENDENCE

ARAVA has no known potential for abuse or dependence.

OVERDOSAGE

There is no human experience regarding leflunomide overdosage. In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200–500 mg/kg and 100 mg/kg, respectively (approximately >350 times the maximum recommended human dose, respectively).

In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination (see PRECAUTIONS—General—Need for Drug Elimination).

DOSAGE AND ADMINISTRATION

Loading Dose

Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.

Maintenance Therapy

Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n=104), treated with 25 mg/day, experienced a greater incidence of side effects; alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes should be monitored and dose adjustments may be necessary (see WARNINGS—Hepatotoxicity). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA Tablets in 10 and 20 mg strengths are packaged in bottles. ARAVA Tablets 100 mg strength are packaged in blister packs.

[See table above]

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only.

Prescribing Information as of April 2000A

Continued on next page

PHYSICIANS' DESK REFERENCE®

Executive Vice President, PDR: David Duplay

Vice President, Sales and Marketing: Dikran N. Barsamian
Senior Director, Pharmaceutical Sales: Anthony Sorce
National Account Manager: Marion Reid, RPh
Senior Account Managers: Frank Karkowsky, Suzanne E. Yarrow, RN
Account Managers: Marjorie A. Jaxel, Kevin McGlynn, Elaine Musco, Lois Smith, Elleen Sullivan, Richard Zwickel
Senior Director, Brand and Product Management: Valerie E. Berger
Director, Brand and Product Management: Carmen Mazzatta
Associate Product Managers: Michael Casale, Andrea Colavecchio
Senior Director, Publishing Sales and Marketing: Michael Bennett
Director of Trade Sales: Bill Gaffney
Associate Director of Marketing: Jennifer M. Fronzaglia
Senior Marketing Manager: Kim Marich
Direct Mail Manager: Lorraine M. Loening
Manager of Marketing Analysis: Dina A. Maeder
Promotion Manager: Linda Levine
Vice President, Regulatory Affairs: Mukesh Mehta, RPh
Vice President, PDR Services: Brian Holland
Director of PDR Operations: Jeffrey D. Schaefer
Director of Operations: Robert Klein
Clinical Content Operations Manager: Thomas Fleming, PharmD

Manager, Editorial Services: Bette LaGow
Drug Information Specialists: Min Ko, PharmD; Greg Tallis, RPh
Project Editors: Neil Chesanow, Harris Fleming
Senior Editor: Lori Murray
Production Editor: Gwynned L. Kelly
Manager, Production Purchasing: Thomas Westburgh
Production Manager: Gayle Greizzaro
Production Specialist: Christina Klinger
Senior Production Coordinator: Gianna Caradonna
Production Coordinator: Yasmin Hernández
Senior Index Editors: Noel Deloughery, Shannon Reilly
Format Editor: Michelle S. Guzman
Traffic Assistant: Kim Condon
PDR Sales Coordinators: Nick W. Clark, Gary Lew
Production Design Supervisor: Adeline Rich
Senior Electronic Publishing Designer: Livio Udina
Electronic Publishing Designers: Bryan C. Dix, Rosalia Sbema
Production Associate: Joan K. Akerlind
Digital Imaging Manager: Christopher Husted
Digital Imaging Coordinator: Michael Labruyere
Finance Director: Mark S. Ritchin
Director of Client Services: Stephanie Struble

ISBN: 1-56363-497-X

DOSAGE AND ADMINISTRATION

Loading Dose

Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days. Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of hematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past. (See WARNINGS—Hepatotoxicity).

Maintenance Therapy

Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n=104), treated with 25 mg/day, experienced a greater incidence of side effects; alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes must be monitored and dose adjustments may be necessary (see WARNINGS—Hepatotoxicity). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA Tablets in 10 and 20 mg strengths are packaged in bottles. ARAVA Tablets 100 mg strength are packaged in blister packs.

[See second table on previous page]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature). Protect from light.

Rx only.

Rev. March 2004

Manufactured by

Usiphar, 60200 Compiegne, France

for

Aventis Pharmaceuticals Inc.

Kansas City, MO 64137

Made in France

Shown in Product Identification Guide, page 307

CLAFORAN®

℞

[kla 'for-an]

Sterile (cefotaxime for injection, USP)

and Injection (cefotaxime injection, USP)

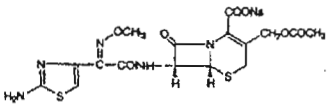
Rx only

Prescribing Information as of January 2004

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CLAFORAN® (cefotaxime sodium) and other antibacterial drugs, CLAFORAN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Sterile CLAFORAN® (cefotaxime sodium) is a semisynthetic, broad spectrum cephalosporin antibiotic for parenteral administration. It is the sodium salt of 7-[2-(2-amino-4-thiazolyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate 7[2] (Z)-(o-methyloxime), acetate (ester). CLAFORAN contains approximately 50.5 mg (2.2 mEq) of sodium per gram of cefotaxime activity. Solutions of CLAFORAN range from very pale yellow to light amber depending on the concentration and the diluent used. The pH of the injectable solutions usually ranges from 5.0 to 7.5. The CAS Registry Number is 64485-93-4.



CLAFORAN is supplied as a dry powder in conventional and ADD-Vantage® System compatible vials, infusion bottles, pharmacy bulk package bottles, and as a frozen, premixed, iso-osmotic injection in a buffered diluent solution in plastic containers. CLAFORAN, equivalent to 1 gram and 2 grams cefotaxime, is supplied as frozen, premixed, iso-osmotic injections in plastic containers. Solutions range from very pale yellow to light amber. Dextrose Hydrous, USP has been added to adjust osmolality (approximately 1.7 g and 700 mg to the 1 g and 2 g cefotaxime dosages, respectively). The injections are buffered with sodium citrate hydrous, USP. The pH is adjusted with hydrochloric acid and may be adjusted with sodium hydroxide.

The plastic container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Following IM administration of a single 500 mg or 1 g dose of CLAFORAN to normal volunteers, mean peak serum concentrations of 11.7 and 20.5 mcg/mL respectively were attained within 30 minutes and declined with an elimination half-life of approximately 1 hour. There was a dose-dependent increase in serum levels after the IV administration of 500 mg, 1 g, and 2 g of CLAFORAN (38.9, 101.7, and 214.4 mcg/mL respectively) without alteration in the elimination half-life. There is no evidence of accumulation following repetitive IV infusion of 1 g doses every 6 hours for 14 days as there are no alterations of serum or renal clearance. About 60% of the administered dose was recovered from urine during the first 6 hours following the start of the infusion.

Approximately 20-36% of an intravenously administered dose of ^{14}C-cefotaxime is excreted by the kidney as unchanged cefotaxime and 15–25% as the desacetyl derivative, the major metabolite. The desacetyl metabolite has been shown to contribute to the bactericidal activity. Two other urinary metabolites (M_2 and M_3) account for about 20-25%. They lack bactericidal activity.

A single 50 mg/kg dose of CLAFORAN was administered as an intravenous infusion over a 10- to 15-minute period to 23 newborn infants grouped according to birth weight and age. The mean half-life of cefotaxime in infants with lower birth weights (≤1500 grams), regardless of age, was longer (4.8 hours) than the mean half-life (3.4 hours) in infants whose birth weight was greater than 1500 grams. Mean serum clearance was also smaller in the lower birth weight infants. Although the differences in mean half-life values are statistically significant for weight, they are not clinically important. Therefore, dosage should be based solely on age. (See DOSAGE AND ADMINISTRATION section.)

Additionally, no disulfiram-like reactions were reported in a study conducted in 22 healthy volunteers administered CLAFORAN and ethanol.

Microbiology

The bactericidal activity of cefotaxime sodium results from inhibition of cell wall synthesis. Cefotaxime sodium has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Cefotaxime sodium has a high degree of stability in the presence of β-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Cefotaxime sodium has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobes, Gram-positive:

Enterococcus spp.

*Staphylococcus aureus**, including β-lactamase-positive and negative strains

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus pyogenes (Group A beta-hemolytic streptococci)

Streptococcus spp.

---

*Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to cefotaxime sodium.

Aerobes, Gram-negative:

Acinetobacter spp.

Citrobacter spp.

Enterobacter spp.

Escherichia coli

Haemophilus influenzae (including ampicillin-resistant strains)

Haemophilus parainfluenzae

Klebsiella spp. (including *Klebsiella pneumoniae*)

Morganella morganii

Neisseria gonorrhoeae (including β-lactamase-positive and negative strains)

Neisseria meningitidis

Proteus mirabilis

Proteus vulgaris

Providencia retigeri

Providencia stuartii

Serratia marcescens

NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, e.g. penicillins, cephalosporins, and aminoglycosides, are susceptible to cefotaxime sodium. Cefotaxime sodium is active against some strains of *Pseudomonas aeruginosa*.

Anaerobes:

Bacteroides spp., including some strains of *Bacteroides fragilis*

Clostridium spp. (Note: Most strains of *Clostridium difficile* are resistant.)

Fusobacterium spp. (including *Fusobacterium nucleatum*).

Peptococcus spp.

Peptostreptococcus spp.

Cefotaxime sodium also demonstrates *in vitro* activity against the following microorganisms but the clinical significance is unknown. Cefotaxime sodium exhibits *in vitro* minimal inhibitory concentrations (MICs) of 8 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefotaxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Aerobes, Gram-negative:

Providencia spp.

Salmonella spp. (including *Salmonella typhi*)

Shigella spp.

Cefotaxime sodium is highly stable *in vitro* to four of the five major classes of β-lactamases described by Richmond et al.[1], including type IIIa (TEM) which is produced by many gram-negative bacteria. The drug is also stable to β-lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime sodium shows high affinity for penicillin-binding proteins in the cell wall, including PBP: Ib and III.

Cefotaxime sodium and aminoglycosides have been shown to be synergistic *in vitro* against some strains of *Pseudomonas aeruginosa* but the clinical significance is unknown.

Susceptibility Tests

Dilution techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[1] (broth or agar) or equivalent with cefotaxime sodium powder. The MIC values obtained should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp.

MIC (mcg/mL)	Interpretation:
≤8	Susceptible (S)
16-32	Intermediate (I)
≥64	Resistant (R)

When testing *Haemophilus* spp.[b]

MIC (mcg/mL)	Interpretation[c]
≤2	Susceptible (S)

When testing *Streptococcus*[d]

MIC (mcg/mL)	Interpretation
≤0.5	Susceptible (S)
1	Intermediate (I)
≥2	Resistant (R)

When testing *Neisseria gonorrhoeae*[e]

MIC (mcg/mL)	Interpretation[c]
≤0.5	Susceptible (S)

---

a. Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.

b. Interpretive criteria is applicable only to tests performed by broth microdilution method using Haemophilus Test Media.[3]

c. The absence of resistant strains precludes defining any interpretations other than susceptible.

d. *Streptococcus pneumoniae* must be tested using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

e. Interpretive criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.[2]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal and if the microorganism is not fully susceptible to alternative clinically feasible drugs the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable, other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedure. Standard cefotaxime sodium powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	0.06-0.25
Staphylococcus aureus ATCC 29213	1-4
Pseudomonas aeruginosa ATCC 27853	4-16
Haemophilus influenzae[a] ATCC 49247	0.12-0.5
Streptococcus pneumoniae[b] ATCC 49619	0.06-0.25
Neisseria gonorrhoeae[c] ATCC 49226	0.015-0.06

---

a. Ranges applicable only to tests performed by broth microdilution method using Haemophilus Test Media.[3]

b. Ranges applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2–5% lysed horse blood.[3]

c. Ranges applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.[2]

Continued on next page

B

AventisPharmaceuticals

Aventis

IMPORTANT PRODUCT INFORMATION

ARAVA® (LEFLUNOMIDE) 100 MG TABLETS DISCONTINUED

January 4, 2002

Dear Pharmaceutical Buyer:

Aventis Pharmaceuticals has made a decision to discontinue 100 mg Arava® (leflunomide) tablets trade package. Following is information on the affected product:

NDC Number	Product Description/Size
0088-2162-03	100 mg, 3-ct blister pack

This discontinuation will take effect immediately and will affect only this trade size. We will continue to offer Arava in the 10- and 20- mg tablet size.

For returns on this product, note that if the product dating falls within the expiration date of the Aventis return policy, then return product to our designated return service, One-Box. If the product dating falls outside of the Aventis return policy dating, then contact our Customer Service Department for return authorization at 1-800-207-8049.

If you have any questions please feel free to contact your Aventis Pharmaceuticals Senior National Trade Account Manager or our Customer Service Department.

Sincerely,

Guerdon R. Green
Director, Trade Administration & Development
Managed Healthcare
ARA-LT-988-1

C

Initiation Dose Request

To obtain initiation doses of Arava for your patients, complete the "Requests for Initiation Doses of Arava (leflunomide)" form online. Follow the instructions below on completing the form. Then, click the "Click to Proceed" button at the bottom of the page to access the form.

1. To complete the form, type in the requested information, and click the "Submit" button when you're finished.
2. This page will display the information you provided so you may review it for accuracy. If you need to make changes, click the "Back" button. If all your information is correct, click the "Print" button.
3. Sign the completed, printed form and mail it to:

Aventis Pharmaceuticals
Arava: Initiation Dose Request
5870 Trinity Parkway, Suite 600
Centreville, VA 20120-1970

→ Requests for Initiation Doses of Arava Online Form

D

Department of Health and Human Services | Public Health Service

Food and Drug Administration
Rockville, MD 20857

JAN 8 2002

INVOICE ENCLOSED

User Fee Invoice Enclosed – Products and Establishments

Dear Colleague:

This communication contains an invoice (Attachment A) under the Prescription Drug User Fee Act of 1992 (PDUFA) as amended by the Food and Drug Administration Modernization Act of 1997 (Modernization Act).[1] This invoice is for fiscal year (FY) 2002[2] applicable product or establishment fees assessed to your firm. Instructions for payment are included in Attachment B. **Payment is due by January 31, 2002, without regard to whether you intend to request a waiver or fee reduction.**

FDA has established the annual fees for products and establishments based upon the provisions of the Modernization Act that provide for adjustment of the annual fees based on inflation and workload. Before the end of this year, FDA will publish a notice in the *Federal Register* providing the adjusted rates and a description of how they were derived.

If you identify other products or establishments for which you have not been billed and for which you believe your firm should be assessed fees for FY 2002, or if you have any questions concerning the attached invoice, please contact Beverly Friedman or Michael Jones at:

Center for Drug Evaluation and Research
Food and Drug Administration, HFD-5
5600 Fishers Lane
Rockville, MD 20857
301-594-2041
FAX: 301-827-5562

RECEIVED
JAN 15 2002
REGULATORY AFFAIRS

Information on PDUFA as amended by the Modernization Act is available at www.fda.gov/cder/pdufa/default.htm.

We appreciate your continued cooperation and thank you in advance for your prompt payment.

Sincerely,

Helen S. Horn

Helen S. Horn, Acting Director
Office of Financial Management

Enclosures:
Attachment A – Product/Establishment Fee Invoice
Attachment B – Payment Instructions

[1] Sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379g and 379h).
[2] FY 2002 = October 1, 2001 through September 30, 2002

ATTACHMENT A

FDA

FOOD AND DRUG ADMINISTRATION

INVOICE

Bill Number : 999466

Billing Date : 20-DEC-2001

Make Remittance Payable To and Mail To :

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
Pittsburgh, PA 15251-6909

Payments sent by private courier must be addressed to:

FOOD AND DRUG ADMINISTRATION (360909)
Mellon Client Service Center Rm 670
500 Ross Street
Pittsburgh, PA 15262-0001

AVENTIS PHARMACEUTICALS INC

10236 MARION PARK DR MAIL CODE J5M1540
KANSAS CITY MO 64137

Type of Fee (Product, Establishment)	Number of Products or Establishments	Unit Fee	Total
Product	39	$ 21,630.00	$ 843,570.00
Establishment	5.158	$140,109.00	$ 722,682.22
		Total Fee :	$ 1,566,252.22

Payment must be received by the U.S. Food and Drug Administration before January 31, 2002, in U.S. dollars, by check, bank draft, or U. S. Postal money order payable to the order of the U.S. Food and Drug Administration, and any check or bank draft should be drawn on or payable through U.S. financial institutions located in the United States.

If full payment is not received by January 31, 2002, an interest rate of 13.25% will be charged. In addition, delinquent invoices will be assessed a $20 administrative fee for each full 30 day period that the account remains outstanding. A 6% late payment penalty fee also will be charged as stated in 45 CFR Subtitle A, Section 30.13.

A receipt will be issued upon request. The invoice will not be considered paid until payment has been cleared and the amount received by the U.S. Food and Drug Administration.

For further information concerning this invoice, please contact Beverly Friedman at 301-594-2041

Billing Firm: AVENTIS PHARMACEUTICALS INC 72223

>>>> DRUG PRODUCTS <<<<

NDA/PRODUCT	TRADE NAME	DOSAGE; ROUTES OF ADMIN.
N020905 003	ARAVA	TABLET; ORAL
Ingredient		Potency
LEFLUNOMIDE		100MG
N021022 001	PENLAC	SOLUTION; TOPICAL
Ingredient		Potency
CICLOPIROX		8%
N021024 001	PRIFTIN	TABLET; ORAL
Ingredient		Potency
RIFAPENTINE		150MG
N021081 001	LANTUS	INJECTABLE; SUBCUTANEOUS
Ingredient		Potency
INSULIN GLARGINE		100UNT/1ML
N050547 001	CLAFORAN	POWDER, FOR INJECTION SOLUTION; IV(INFUSION)
Ingredient		Potency
CEFOTAXIME SODIUM		EQ 500MG BASE/VIAL
N050547 004	CLAFORAN	POWDER, FOR INJECTION SOLUTION; IV(INFUSION)
Ingredient		Potency
CEFOTAXIME SODIUM		EQ 10GM BASE/VIAL
N050596 001	CLAFORAN IN SODIUM CHLORIDE 0.9%	INJECTION; IV(INFUSION)
Ingredient		Potency
CEFOTAXIME SODIUM		EQ 20MG BASE/ML
N050596 002	CLAFORAN IN DEXTROSE 5%	INJECTION; IV(INFUSION)
Ingredient		Potency
CEFOTAXIME SODIUM		EQ 20MG BASE/ML
N050596 003	CLAFORAN IN SODIUM CHLORIDE 0.9%	INJECTION; IV(INFUSION)
Ingredient		Potency
CEFOTAXIME SODIUM		EQ 40MG BASE/ML

Department of Health and Human Services — Public Health Service

Food and Drug Administration
Rockville, MD 20857

INVOICE ENCLOSED

User Fee Invoice Enclosed – Products and Establishments AUG 15 2002

Dear Colleague:

On June 12, 2002, the President signed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which includes the Prescription Drug User Fee Amendments of 2002 (PDUFA III). PDUFA III authorizes the Food and Drug Administration (FDA) to continue to collect three types of user fees from applicants who submit certain new drug and biological product applications and supplements and for certain products and establishments.[1] These amendments to the Federal Food, Drug, and Cosmetic Act (the Act) provide increased resources for FDA to implement improvements in the drug and biological product review processes and conduct risk management activities for these products. The following documents are enclosed:

Attachment A: An invoice for the annual product and/or establishment fees assessed to your company for fiscal year 2003 (FY 2003)[2] under the user fee provisions of the Act. FDA has established the annual fees for products and establishments based on the provisions of PDUFA III that provide for adjustment of the annual fees based on inflation and workload. On August 2, 2002, FDA published a Notice in the *Federal Register* (67 FR 50448) providing the adjusted rates and a description of how they were calculated.[3]

Attachment B: Instructions for payment. **Payment is due by October 1, 2002, without regard to whether you intend to request a waiver or fee reduction.**

If you identify other products or establishments for which you have not been billed and for which you believe your firm should be assessed user fees for FY 2003, or if you have any questions concerning the attached invoice, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at:

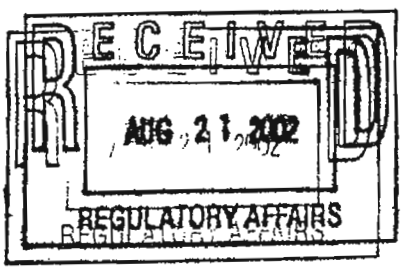
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-5
5600 Fishers Lane
Rockville, MD 20857
Phone: 301-594-2041 or Fax: 301-827-5562

Information on prescription drug user fees is available at www.fda.gov/cder/pdufa/default.htm.
We appreciate your continued cooperation and thank you in advance for your prompt payment.

Sincerely,

Helen S. Horn

Helen S. Horn, Acting Director
Office of Financial Management



Enclosures:
Attachment A – Product/Establishment Fee Invoice
Attachment B – Payment Instructions

[1] Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h) as amended by PDUFA III.
[2] FY 2003 = October 1, 2002, through September 30, 2003.
[3] Available on the Internet at http://www.fda.gov/cder/pdufa/default.htm under Federal Register Documents.

ATTACHMENT A

FDA

FOOD AND DRUG ADMINISTRATION

INVOICE

Bill Number : 1000489

Billing Date : 15-AUG-2002

Make Remittance Payable To and Mail To :

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
Pittsburgh, PA 15251-6909

Payments sent by private courier must be addressed to:

FOOD AND DRUG ADMINISTRATION (360909)
Mellon Client Service Center Rm 670
500 Ross Street
Pittsburgh, PA 15262-0001

RECEIVED
AUG 21 2002
REGULATORY AFFAIRS

AVENTIS PHARMACEUTICALS INC

10236 MARION PARK DR MAIL CODE J5M1540
KANSAS CITY MO 64137

Type Of Fee (Product/Establishment)	Number Of Products or Establishments	Unit Fee	Total
Product	55	$ 32,400.00	$1,782,000.00
Establishment	11.035	$209,900.00	$2,316,246.50
		Total Fee :	$ 4,098,246.50

Payment must be received by the U.S. Food and Drug Administration by October 1, 2002, in U.S. dollars, by check, bank draft, or U.S. Postal money order payable to the order of the U.S. Food and Drug Administration, and any check or bank draft should be drawn on or payable through U.S. financial institutions located in the United States.

If full payment is not received by October 1, 2002, an interest rate of 12.625% will be charged. In addition, delinquent invoices will be assessed a $20 administrative fee for each full 30 day period that the account remains outstanding. A 6% late payment penalty fee also will be charged as stated in 45 CFR Subtitle A, Section 30.13.

A receipt will be issued upon request. The invoice will not be considered paid until payment has been cleared and the amount received by the U.S. Food and Drug Administration.

For further information concerning this invoice, please contact Beverly Friedman at 301-594-2041

Billing Firm:	AVENTIS PHARMACEUTICALS INC	72223

Owner of Products: AVENTIS PHARMACEUTICALS INC 72223

NDA #/Prod #		Trade Name/Ingredient	Dosage Form/Strength
20623	2	ANZEMET	Tablet; Oral
		DOLASETRON MESYLATE MONOHYDRATE	EQ 100MG BASE
20624	1	ANZEMET	Injectable; Injection
		DOLASETRON MESYLATE MONOHYDRATE	EQ 20MG BASE/ML
20625	1	ALLEGRA	Capsule; Oral
		FEXOFENADINE HYDROCHLORIDE	60MG
20786	1	ALLEGRA-D	Tablet, Extended Release; Oral
		FEXOFENADINE HYDROCHLORIDE; PSEUDOEPHED	60MG;120MG
20872	1	ALLEGRA	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	30MG
20872	2	ALLEGRA	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	60MG
20872	4	ALLEGRA	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	180MG
20905	1	ARAVA	Tablet; Oral
		LEFLUNOMIDE	10MG
20905	2	ARAVA	Tablet; Oral
		LEFLUNOMIDE	20MG
20905	3	ARAVA	Tablet; Oral
		LEFLUNOMIDE	100MG
21024	1	PRIFTIN	Tablet; Oral
		RIFAPENTINE	150MG

Department of Health and Human Services — Public Health Service

Food and Drug Administration
Rockville, MD 20857

AUG 15 2003

INVOICE ENCLOSED

User Fee Invoice Enclosed – Products and Establishments

Dear Colleague:

On June 12, 2002, the President signed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which includes the Prescription Drug User Fee Amendments of 2002 (PDUFA III). PDUFA III authorizes the Food and Drug Administration (FDA) to continue to collect three types of user fees from applicants who submit certain new drug and biological product applications and supplements and for certain products and establishments.[1] These amendments to the Federal Food, Drug, and Cosmetic Act (the Act) provide increased resources for FDA to implement improvements in the drug and biological product review processes and conduct risk management activities for these products. The following documents are enclosed:

Attachment A: An invoice for the annual product and/or establishment fees assessed to your company for fiscal year 2004 (FY 2004)[2] under the user fee provisions of the Act. FDA has established the annual fees for products and establishments based on the provisions of PDUFA III that provide for adjustment of the annual fees based on inflation and workload. On August 1, 2003, FDA published a Notice in the *Federal Register* (68 FR 45249) providing the adjusted rates and a description of how they were calculated.[3]

Attachment B: Instructions for payment. **Payment is due by October 1, 2003, without regard to whether you intend to request a waiver or fee reduction.**

If you identify other products or establishments for which you have not been billed and for which you believe your firm should be assessed user fees, or if you have any questions concerning the attached invoice, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at:

Phone: 301-594-2041
FAX: 301-827-5562

Information on prescription drug user fees is available at www.fda.gov/cder/pdufa/default.htm.
We appreciate your continued cooperation and thank you in advance for your prompt payment.

Sincerely,

for Helen S. Horn, Director
Office of Financial Management

RECEIVED
AUG 18 2003
REGULATORY AFFAIRS

Enclosures:
Attachment A – Product/Establishment Fee Invoice
Attachment B – Payment Instructions

[1] Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h) as amended by PDUFA III.
[2] FY 2004 = October 1, 2003, through September 30, 2004.
[3] Available on the Internet at http://www.fda.gov/cder/pdufa/default.htm under Federal Register Documents.

ATTACHMENT A

FDA

FOOD AND DRUG ADMINISTRATION

INVOICE

Bill Number : 1001969

Billing Date : 15-AUG-2003

Make Remittance Payable To and Mail To :

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
Pittsburgh, PA 15251-6909

Payments sent by private courier must be addressed to:

FOOD AND DRUG ADMINISTRATION (360909)
Mellon Client Service Center Rm 670
500 Ross Street
Pittsburgh, PA 15262-0001

AVENTIS PHARMACEUTICALS INC

10236 MARION PARK DR MAIL CODE J5M1540
KANSAS CITY MO 64137

RECEIVED
AUG 18 2003
REGULATORY AFFAIRS

Type Of Fee (Product, Establishment)	Number Of Products or Establishments	Unit Fee	Total
Product	55	$ 36,080.00	$1,984,400.00
Establishment	11.763	$226,800.00	$2,667,848.40
		Total Fee :	$ 4,652,248.40

Payment must be received by the U.S. Food and Drug Administration by October 1, 2003, in U.S. dollars, by check, bank draft, or U.S. Postal money order payable to the order of the U.S. Food and Drug Administration, and any check or bank draft should be drawn on or payable through U.S. financial institutions located in the United States.

If full payment is not received by October 1, 2003, an interest rate of 12.125% will be charged. In addition, delinquent invoices will be assessed a $20 administrative fee for each full 30 day period that the account remains outstanding. A 6% late payment penalty fee also will be charged as stated in 45 CFR Subtitle A, Section 30.13.

A receipt will be issued upon request. The invoice will not be considered paid until payment has been cleared and the amount received by the U.S. Food and Drug Administration.

For further information concerning this invoice, please contact Beverly Friedman at 301-594-2041

Billing Firm:	AVENTIS PHARMACEUTICALS INC	72223

Owner of Products: AVENTIS PHARMACEUTICALS INC 72223

NDA #/Prod #		Trade Name/Ingredient	Dosage Form/Strength
20624	1	ANZEMET	Injectable; Injection
		DOLASETRON MESYLATE MONOHYDRATE	EQ 20MG BASE/ML
20624	2	ANZEMET	Injectable; Injection
		DOLASETRON MESYLATE MONOHYDRATE	EQ 12.5MG BASE/ML
20625	1	ALLEGRA	Capsule; Oral
		FEXOFENADINE HYDROCHLORIDE	60MG
20786	1	ALLEGRA-D	Tablet, Extended Release; Oral
		FEXOFENADINE HYDROCHLORIDE; PSEUDOEPHED	60MG;120MG
20872	1	ALLEGRA	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	30MG
20872	2	ALLEGRA	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	60MG
20872	4	ALLEGRA	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	180MG
20905	1	ARAVA	Tablet; Oral
		LEFLUNOMIDE	10MG
20905	2	ARAVA	Tablet; Oral
		LEFLUNOMIDE	20MG
20905	3	ARAVA	Tablet; Oral
		LEFLUNOMIDE	100MG
21024	1	PRIFTIN	Tablet; Oral
		RIFAPENTINE	150MG

Department of Health and Human Services Public Health Service

Food and Drug Administration
Rockville, MD 20857

AUG 12 2004

INVOICE ENCLOSED

User Fee Invoice Enclosed – FY 2005 Products and Establishments

Dear Colleague:

On June 12, 2002, the President signed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which includes the Prescription Drug User Fee Amendments of 2002 (PDUFA III). PDUFA III authorizes the Food and Drug Administration (FDA) to continue to collect three types of user fees from applicants who submit certain new drug and biological product applications and supplements and for certain products and establishments.[1] These amendments to the Federal Food, Drug, and Cosmetic Act (the Act) provide increased resources for FDA to implement improvements in the drug and biological product review processes and conduct risk management activities for these products. The following documents are enclosed:

Attachment A: An invoice for the annual product and/or establishment fees assessed to your company for fiscal year (FY) 2005[2] under the user fee provisions of the Act. FDA has established the annual fees for products and establishments based on the provisions of PDUFA III that provide for adjustment of the annual fees based on inflation and workload. On August 2, 2004, FDA published a notice in the *Federal Register* (69 FR 46165) providing the adjusted rates and a description of how they were calculated.[3]

Attachment B: Instructions for payment. **Payment is due by October 1, 2004, without regard to whether you intend to request a waiver or fee reduction.**

If you identify other products or establishments for which you have not been billed and for which you believe your firm should be assessed user fees, or if you have any questions concerning the attached invoice, please contact Beverly Friedman or Michael Jones at:

Phone: 301-594-2041
FAX: 301-827-5562

Information on prescription drug user fees is available at www.fda.gov/cder/pdufa/default.htm. We appreciate your continued cooperation and thank you in advance for your prompt payment.

Sincerely,

Helen S. Horn

Helen S. Horn, Director
Office of Financial Management

RECEIVED
AUG 20 2004
REGULATORY AFFAIRS

Enclosures:
Attachment A – Product/Establishment Fee Invoice
Attachment B – Payment Instructions

[1] Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h) as amended by PDUFA III.
[2] FY 2005 = October 1, 2004, through September 30, 2005.
[3] Available on the Internet at http://www.fda.gov/cder/pdufa/default.htm under Federal Register Documents.

ATTACHMENT A

FDA

FOOD AND DRUG ADMINISTRATION

INVOICE

Bill Number : 1002471

Billing Date : 12-AUG-2004

Make Remittance Payable To and Mail To :

FOOD AND DRUG ADMINISTRATION
P.O. BOX 360909
Pittsburgh, PA 15251-6909

Payments sent by private courier must be addressed to:

FOOD AND DRUG ADMINISTRATION (360909)
Mellon Client Service Center Rm 670
500 Ross Street
Pittsburgh, PA 15262-0001

AVENTIS PHARMACEUTICALS INC

10236 MARION PARK DR MAIL CODE J5M1540
KANSAS CITY MO 64137

Type Of Fee (Product, Establishment)	Number Of Products for Establishments	Unit Fee	Total
Product	48	$ 41,710.00	$2,002,080.00
Establishment	9.023	$262,200.00	$2,365,830.60
		Total Fee :	$ 4,367,910.60

Payment must be received by the U.S. Food and Drug Administration by October 1, 2004, in U.S. dollars, by check, bank draft, or U.S. Postal money order payable to the order of the U.S. Food and Drug Administration. Any check or bank draft should be drawn on or payable through U.S. financial institutions located in the United States.

If full payment is not received by October 1, 2004, an interest rate of 11-7/8% will be charged. In addition, delinquent invoices will, for each 30 day period that the account remains outstanding, have a $20 administrative fee assessed. A penalty charge of 6% per year will be assessed on any invoices delinquent for more than 90 days in accordance with 45 CFR Subtitle A, Section 30.13.

Receipts will be issued upon request. This invoice will not be considered paid until payment has been cleared and the amount received by the U.S. Food and Drug Administration.

For further information concerning this invoice, please contact Beverly Friedman at 301-594-2041

Billing Firm:	AVENTIS PHARMACEUTICALS INC	72223

Owner of Products: AVENTIS PHARMACEUTICALS INC 72223

NDA #/Prod #		Trade Name/Ingredient	Dosage Form/Strength
20624	3	ANZEMET	INJECTABLE; INJECTION
		DOLASETRON MESYLATE MONOHYDRATE	EQ 500MG BASE/25ML
20625	1	ALLEGRA	CAPSULE; ORAL
		FEXOFENADINE HYDROCHLORIDE	60MG
20784	1	NASACORT HFA	SPRAY, METERED; NASAL
		TRIAMCINOLONE ACETONIDE	0.055MG/SPRAY
20786	1	ALLEGRA-D	TABLET, EXTENDED RELEASE; ORAL
		FEXOFENADINE HYDROCHLORIDE; PSEUDOEPHED	60MG;120MG
20872	1	ALLEGRA	TABLET; ORAL
		FEXOFENADINE HYDROCHLORIDE	30MG
20872	2	ALLEGRA	TABLET; ORAL
		FEXOFENADINE HYDROCHLORIDE	60MG
20872	4	ALLEGRA	TABLET; ORAL
		FEXOFENADINE HYDROCHLORIDE	180MG
20905	1	ARAVA	TABLET; ORAL
		LEFLUNOMIDE	10MG
20905	2	ARAVA	TABLET; ORAL
		LEFLUNOMIDE	20MG
20905	3	ARAVA	Tablet; Oral
		LEFLUNOMIDE	100MG
21024	1	PRIFTIN	TABLET; ORAL
		RIFAPENTINE	150MG

DEPARTMENT OF HE. H & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

May 5, 2005

Dear Colleague:

The Federal Food, Drug, and Cosmetic Act (the Act) authorizes the Food and Drug Administration (FDA) to collect annual user fees for certain products and establishments.[1] We plan to issue the fiscal year (FY) 2006[2] product and establishment invoices in August 2005,[3] and the fees will be due on October 1, 2005. To prepare for the FY 2006 invoices, we are asking for your assistance in updating our records. Please provide the following information for your company: (1) contact for user fee invoices (Attachment A) and (2) a list of products and establishments subject to user fees (Attachment B). In addition, this year we are asking firms with biologic products to update Attachment B with the brand names[4] of your products so that the brand names may be included on future invoices. See section II.B below for instructions.

I. What Is Attached to This Letter?

Attachment A shows the contact information of the person designated by your company to receive correspondence, invoices, and inquiries concerning user fees. Attachment B is a list of the products and establishments for which you were assessed fees in FY 2005. This list contains all products and establishments that appeared on your FY 2005 invoice issued in August 2004.

II. What Information Does FDA Need to Ensure an Accurate Invoice for FY 2006?

To ensure that the FY 2006 product and establishment fees are accurately assessed under the Act, we ask that you provide the information described in the following subsections.

A. Attachment A - User Fee Contact Information

Review the contact information that we have on Attachment A and make any necessary additions or corrections. Then sign the attachment. Include your title and date.

---

[1] See Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h). The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 amended the Act and authorized FDA to collect fees through September 30, 2007. We described the technical amendments to the Act in a letter dated June 12, 2002. If you wish to view that June 12, 2002, *Dear Colleague* letter, go to www.fda.gov/cder/pdufa/default.htm under letters.

[2] FY 2006 = October 1, 2005, to September 30, 2006.

[3] The invoices will be issued after a notice announcing the FY 2006 fees publishes in the *Federal Register*. We do not have an exact date for this publication.

[4] A brand name drug is a drug marketed under a proprietary, trademark-protected name.

Billing Firm:	AVENTIS PHARMACEUTICALS INC	72223

Owner of Products: AVENTIS PHARMACEUTICALS INC 72223

NDA #/Prod #		Trade Name/Ingredient	Dosage Form/Strength
20623	2	ANZEMET mft EST # 16	Tablet; Oral
		DOLASETRON MESYLATE MONOHYDRATE	EQ 100MG BASE
20624	1	ANZEMET mft EST # 16	Injectable; Injection
		DOLASETRON MESYLATE MONOHYDRATE	EQ 20MG BASE/ML
20625	1	ALLEGRA mft Est # 8	Capsule; Oral
		FEXOFENADINE HYDROCHLORIDE	60MG
20786	1	ALLEGRA-D mft Est # 8	Tablet, Extended Release; Oral
		FEXOFENADINE HYDROCHLORIDE; PSEUDOEPHED	60MG;120MG
20872	1	ALLEGRA mft Est # 8	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	30MG
20872	2	ALLEGRA mft Est # 8	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	60MG
20872	4	ALLEGRA mft Est # 8	Tablet; Oral
		FEXOFENADINE HYDROCHLORIDE	180MG
20905	1	ARAVA mft Est # 7	Tablet; Oral
		LEFLUNOMIDE	10MG
20905	2	ARAVA mft Est # 7	Tablet; Oral
		LEFLUNOMIDE	20MG
20905	3	ARAVA mft Est # 7	Tablet; Oral
		LEFLUNOMIDE	100MG
21024	1	PRIFTIN mft Est #15	Tablet; Oral
		RIFAPENTINE	150MG

F/U Bill Ind.

E

APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2003.

24th EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2004

LAMOTRIGINE

TABLET; ORAL
LAMICTAL
GLAXOSMITHKLINE 25MG N20241 005 DEC 27, 1994
100MG N20241 001 DEC 27, 1994
150MG N20241 002 DEC 27, 1994
+ 200MG N20241 003 DEC 27, 1994

TABLET, CHEWABLE; ORAL
LAMICTAL CD
GLAXOSMITHKLINE 2MG N20764 004 SEP 08, 2000
5MG N20764 001 AUG 24, 1998
+ 25MG N20764 002 AUG 24, 1998

LANSOPRAZOLE

CAPSULE, DELAYED REL PELLETS; ORAL
PREVACID
TAP PHARM 15MG N20406 001 MAY 10, 1995
+ 30MG N20406 002 MAY 10, 1995

FOR SUSPENSION, EXTENDED RELEASE; ORAL
PREVACID
TAP PHARM 15MG/PACKET N21281 001 MAY 03, 2001
+ 30MG/PACKET N21281 002 MAY 03, 2001

TABLET, ORALLY DISINTEGRATING; ORAL
PREVACID
TAP PHARM 15MG N21428 001 AUG 30, 2002
+ 30MG N21428 002 AUG 30, 2002

LANSOPRAZOLE; *MULTIPLE*
SEE AMOXICILLIN; CLARITHROMYCIN; LANSOPRAZOLE

LANSOPRAZOLE; NAPROXEN

CAPSULE, DELAYED REL PELLETS, TABLET; ORAL
NAPRAPAC 250 (COPACKAGED)
TAP PHARM 15MG,N/A;N/A,250MG N21507 002 NOV 14, 2003
NAPRAPAC 375 (COPACKAGED)
TAP PHARM 15MG,N/A;N/A,375MG N21507 003 NOV 14, 2003
NAPRAPAC 500 (COPACKAGED)
+ TAP PHARM 15MG,N/A;N/A,500MG N21507 [illegible] NOV 14, 2003

LATANOPROST

SOLUTION/DROPS; OPHTHALMIC
XALATAN
+ PHARMACIA AND UPJOHN 0.005% N20597 001 JUN 05, 1996

LEFLUNOMIDE

TABLET; ORAL
ARAVA
AVENTIS PHARMS 10MG N20905 001 SEP 10, 1998
+ 20MG N20905 002 SEP 10, 1998

LEPIRUDIN

INJECTABLE; INJECTION
REFLUDAN
+ BERLEX LABS 50MG/VIAL N20807 001 MAR 06, 1998

LETROZOLE

TABLET; ORAL
FEMARA
+ NOVARTIS 2.5MG N20726 001 JUL 25, 1997

KETOROLAC TROMETHAMINE		
INJECTABLE		
KETOROLAC TROMETHAMINE	30MG/ML	N75230
TABLET		
KETOROLAC TROMETHAMINE	10MG	N74790
KRYPTON, KR-81M		
GAS		
MPI KRYPTON 81M GAS GENERATOR	N/A	N18068
LABETALOL HYDROCHLORIDE		
INJECTABLE		
LABETALOL HCL	5MG/ML	N75355
TABLET		
LABETALOL HCL	100MG	N75223
LABETALOL HCL	200MG	N75223
LABETALOL HCL	300MG	N75223
NORMODYNE	400MG	N18687
TRANDATE	400MG	N18716
LACTULOSE		
SOLUTION		
CEPHULAC	10GM/15ML	N17857
CHRONULAC	10GM/15ML	N17884
DUPHALAC	10GM/15ML	N72372
GENERLAC	10GM/15ML	N71842
LACTULOSE	10GM/15ML	N71841
LACTULOSE	10GM/15ML	N72029
LACTULOSE	10GM/15ML	N73160
LACTULOSE	10GM/15ML	N73590
LACTULOSE	10GM/15ML	N17906
PORTALAC	10GM/15ML	N72374
LAMOTRIGINE		
TABLET		
LAMICTAL	250MG	N20241
LAMICTAL	50MG	N20241
TABLET, CHEWABLE		
LAMICTAL CD	100MG	N20764
LEFLUNOMIDE		
TABLET		
ARAVA	100MG	N20905
LEUCOVORIN CALCIUM		
FOR SOLUTION		
LEUCOVORIN CALCIUM	EQ 60MG BASE/VIAL	N08107
INJECTABLE		
LEUCOVORIN CALCIUM	EQ 3MG BASE/ML	N89352
LEUCOVORIN CALCIUM	EQ 50MG BASE/VIAL	N89353
LEUCOVORIN CALCIUM	EQ 50MG BASE/VIAL	N88939
LEUCOVORIN CALCIUM		
INJECTABLE		
LEUCOVORIN CALCIUM	EQ 100MG BASE/VIAL	N81224
LEUCOVORIN CALCIUM	EQ 50MG BASE/VIAL	N70480
LEUCOVORIN CALCIUM	EQ 3MG BASE/ML	N08107
WELLCOVORIN	EQ 100MG BASE/VIAL	N89834
WELLCOVORIN	EQ 25MG BASE/VIAL	N89833
WELLCOVORIN	EQ 50MG BASE/VIAL	N89465
WELLCOVORIN	EQ 5MG BASE/ML	N87439
TABLET		
LEUCOVORIN CALCIUM	EQ 25MG BASE	N71598
LEUCOVORIN CALCIUM	EQ 5MG BASE	N71600
WELLCOVORIN	EQ 25MG BASE	N18342
WELLCOVORIN	EQ 5MG BASE	N18342
LEUPROLIDE ACETATE		
INJECTABLE		
LUPRON DEPOT-PED	3.75MG/VIAL;7.5MG/VIAL	N20263
LUPRON DEPOT-PED	7.5MG/VIAL;7.5MG/VIAL	N20263
LEVALLORPHAN TARTRATE		
INJECTABLE		
LORFAN	1MG/ML	N10423
LEVAMISOLE HYDROCHLORIDE		
TABLET		
ERGAMISOL	EQ 50MG BASE	N20035
LEVOBETAXOLOL HYDROCHLORIDE		
SUSPENSION/DROPS		
BETAXON	EQ 0.5% BASE	N21114
LEVOCARNITINE		
SOLUTION		
CARNITOR	1GM/10ML	N18948
LEVODOPA		
CAPSULE		
BENDOPA	100MG	N16948
BENDOPA	250MG	N16948
BENDOPA	500MG	N16948
DOPAR	100MG	N16913
DOPAR	250MG	N16913
DOPAR	500MG	N16913
LARODOPA	100MG	N16912
LARODOPA	250MG	N16912
LARODOPA	500MG	N16912
TABLET		
DOPAR	250MG	N16913
DOPAR	500MG	N16913
LARODOPA	100MG	N16912

F

Waterman, Sharon

From: HOLOVACM@cder.fda.gov
Sent: Thursday, July 29, 2004 7:01 AM
To: Jamie.Szturo@sanofi-aventis.com; HOLOVACM@cder.fda.gov
Cc: FRIEDMANB@cder.fda.gov; HARE@cder.fda.gov; JONESM@cder.fda.gov
Subject: Arava

Ms. Szturo,
This was discussed internally and agreed upon that YES, it does fall into "marketing." Please send a letter to the OB staff as detailed below asking us to move it to the active Rx list.
Thank you.
Mary Ann Holovac

-----Original Message-----
From: Jamie.Szturo@aventis.com [mailto:Jamie.Szturo@aventis.com]
Sent: Wednesday, July 28, 2004 2:17 PM
To: HOLOVACM@cder.fda.gov
Cc: FRIEDMANB@cder.fda.gov
Subject: RE: Orange Book Update
Importance: High

-----Original Message-----
From: Szturo, Jamie PH/US
Sent: Tuesday, July 27, 2004 1:09 PM
To: 'Holovac, Mary Ann'
Cc: Friedman, Beverly J
Subject: RE: Orange Book Update

Mary Ann,
This is a "Physician Starter Sample" only - does that fall into 'marketing'?

-----Original Message-----
From: Holovac, Mary Ann [mailto:HOLOVACM@cder.fda.gov]
Sent: Tuesday, July 27, 2004 1:07 PM
To: Szturo, Jamie PH/US; Holovac, Mary Ann
Cc: Friedman, Beverly J
Subject: RE: Orange Book Update

send the OB staff a letter asking us to move it to the Rx section if you are marketing it.

7500 Standish Place
Rockville, MD 20855

Thanks.

-----Original Message-----
From: Jamie.Szturo@aventis.com [mailto:Jamie.Szturo@aventis.com]
Sent: Tuesday, July 27, 2004 2:05 PM
To: HOLOVACM@cder.fda.gov
Cc: FRIEDMANB@cder.fda.gov

Subject: RE: Orange Book Update

Mary Ann,
What do I need to do to have the 100mg moved to active?

-----Original Message-----
From: Holovac, Mary Ann [mailto:HOLOVACM@cder.fda.gov]
Sent: Tuesday, July 27, 2004 12:26 PM
To: Szturo, Jamie PH/US; Holovac, Mary Ann
Cc: Friedman, Beverly J
Subject: RE: Orange Book Update

they are all listed in the Orange Book-the 100mg is on the disc list, the other two potencies on the rx list

-----Original Message-----
From: Jamie.Szturo@aventis.com [mailto:Jamie.Szturo@aventis.com]
Sent: Tuesday, July 27, 2004 12:06 PM
To: holovacm@cder.fda.gov
Cc: friedmanb@cder.fda.gov
Subject: Orange Book Update
Importance: High

Dear Mary Ann,
I am following up with you regarding a phone call I received today from Mrs. Friedman.
I need to confirm that for NDA 20-905 - Arava the following dosages should be listed:
10mg
20mg
100mg

Thank you

Jamie Szturo
Aventis Pharmaceuticals Inc.
US Regulatory CMC - J5-M1540
10236 Marion Park Drive
Kansas City, Mo 64137
816-966-5920
816-966-6794 fax
Nextel 816-564-3560
Jamie.Szturo@aventis.com
Visit RCMC Web: http://draprdwww.brw.hmrag.com/grams/page_item.asp?page_id=23

G

APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

24th EDITION

Cumulative Supplement 7

July 2004

CONTENTS

Please Note:

The 24th Edition of the Orange Book will be the last paper version. All the components of the paper Orange Book are and have been available on the Internet since 1997. Refer to the Introduction 1.3, Availability of the Edition, for specific locations. Additional details will be made available in future Cumulative Supplement publications.

		INJECTABLE; INJECTION						
		KETOROLAC TROMETHAMINE						
AP		HOSPIRA	30MG/ML	N74802	002	Jun 05, 1997	May	CAHN
AP			30MG/ML	N74993	002	Jan 27, 1999	May	CAHN
		TORADOL						
		@ ROCHE PALO	15MG/ML	N19698	001	Nov 30, 1989	Jan	DISC
		@	30MG/ML	N19698	002	Nov 30, 1989	Jan	DISC
		KETOTIFEN FUMARATE						
		SOLUTION/DROPS; OPHTHALMIC						
		ZADITOR						
	+	NOVARTIS	EQ 0.025% BASE	N21066	001	Jul 02, 1999	Feb	CAHN
		LABETALOL HYDROCHLORIDE						
		INJECTABLE; INJECTION						
		LABETALOL HCL						
AP		HOSPIRA	5MG/ML	N75239	001	Nov 29, 1999	May	CAHN
AP			5MG/ML	N75240	001	Nov 29, 1999	May	CAHN
		LAMIVUDINE						
		TABLET; ORAL						
		EPIVIR						
		GLAXOSMITHKLINE	150MG	N20564	001	Nov 17, 1995	May	CRLD
	+		300MG	N20564	003	Jun 24, 2002	May	CRLD
		LAMOTRIGINE						
		TABLET; ORAL						
		LAMICTAL						
	+	GLAXOSMITHKLINE	25MG	N20241	005	Dec 27, 1994	Apr	CRLD
			200MG	N20241	003	Dec 27, 1994	Apr	CRLD
		LANSOPRAZOLE						
>A>		FOR SUSPENSION, DELAYED RELEASE; ORAL						
>A>		PREVACID						
>A>		TAP PHARM	15MG/PACKET	N21281	001	May 03, 2001	Jul	CDFR
>A>	+		30MG/PACKET	N21281	002	May 03, 2001	Jul	CDFR
>D>		FOR SUSPENSION, EXTENDED RELEASE; ORAL						
>D>		PREVACID						
>D>		TAP PHARM	15MG/PACKET	N21281	001	May 03, 2001	Jul	CDFR
>D>	+		30MG/PACKET	N21281	002	May 03, 2001	Jul	CDFR
		INJECTABLE; INTRAVENOUS						
		PREVACID IV						
	+	TAP PHARM	30MG/VIAL	N21566	001	May 27, 2004	May	NEWA
>A>		TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; ORAL						
>A>		PREVACID						
>A>		TAP PHARM	15MG	N21428	001	Aug 30, 2002	Jul	CDFR
>A>	+		30MG	N21428	002	Aug 30, 2002	Jul	CDFR
>D>		TABLET, ORALLY DISINTEGRATING; ORAL						
>D>		PREVACID						
>D>		TAP PHARM	15MG	N21428	001	Aug 30, 2002	Jul	CDFR
>D>	+		30MG	N21428	002	Aug 30, 2002	Jul	CDFR
		LEFLUNOMIDE						
		TABLET; ORAL						
		ARAVA						
>D>		@ AVENTIS PHARMS	100MG	N20905	003	Sep 10, 1998	Jul	CMFD

TABLET; ORAL
ARAVA

>A>		+	AVENTIS PHARMS	100MG	N20905 003	Sep 10, 1998	Jul	CMFD

LEUCOVORIN CALCIUM

INJECTABLE; INJECTION
LEUCOVORIN CALCIUM PRESERVATIVE FREE

>D>	AP		BIGMAR	EQ 200MG BASE/VIAL	N40258 001	Feb 26, 1999	Jul	CAHN
>D>		+		EQ 500MG BASE/VIAL	N40286 001	Feb 26, 1999	Jul	CAHN
>A>	AP		BIGMAR BIOREN PHARMS	EQ 200MG BASE/VIAL	N40258 001	Feb 26, 1999	Jul	CAHN
>A>		+		EQ 500MG BASE/VIAL	N40286 001	Feb 26, 1999	Jul	CAHN
	AP	+	HOSPIRA	EQ 10MG BASE/ML	N40147 001	Jun 25, 1997	May	CAHN

LEVOBUPIVACAINE HYDROCHLORIDE

INJECTABLE; INJECTION
CHIROCAINE

		@	PURDUE PHARMA LP	EQ 2.5MG BASE/ML	N20997 001	Aug 05, 1999	May	DISC
		@		EQ 5MG BASE/ML	N20997 002	Aug 05, 1999	May	DISC
		@		EQ 7.5MG BASE/ML	N20997 003	Aug 05, 1999	May	DISC

LEVOCABASTINE HYDROCHLORIDE

SUSPENSION/DROPS; OPHTHALMIC
LIVOSTIN

		+	NOVARTIS	EQ 0.05% BASE	N20219 001	Nov 10, 1993	Feb	CAHN

LEVOFLOXACIN

SOLUTION/DROPS; OPHTHALMIC
IQUIX

		+	SANTEN	1.5%	N21571 001	Mar 01, 2004	Mar	NEWA

LEVONORGESTREL

TABLET; ORAL
PLAN B

		+	DURAMED	0.75MG	N21045 001	Jul 28, 1999	Feb	CAHN

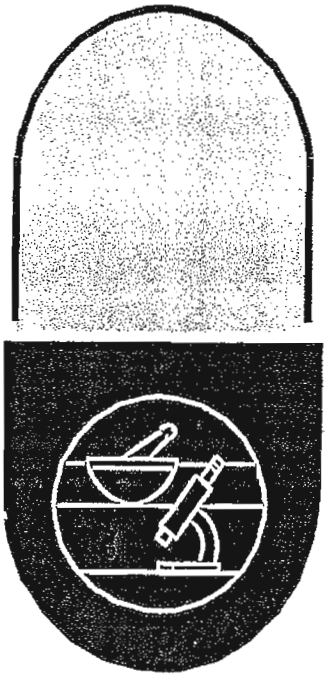
LEVOTHYROXINE SODIUM*

TABLET; ORAL
LEVOLET

>A>	BX		VINTAGE	0.025MG	N21137 001	Jun 06, 2003	Jul	CAHN
>A>	BX			0.05MG	N21137 002	Jun 06, 2003	Jul	CAHN
>A>	BX			0.075MG	N21137 003	Jun 06, 2003	Jul	CAHN
>A>	BX			0.088MG	N21137 004	Jun 06, 2003	Jul	CAHN
>A>	BX			0.1MG	N21137 005	Jun 06, 2003	Jul	CAHN
>A>	BX			0.112MG	N21137 006	Jun 06, 2003	Jul	CAHN
>A>	BX			0.125MG	N21137 007	Jun 06, 2003	Jul	CAHN
>A>	BX			0.137MG	N21137 008	Jun 06, 2003	Jul	CAHN
>A>	BX			0.15MG	N21137 009	Jun 06, 2003	Jul	CAHN
>A>	BX			0.175MG	N21137 010	Jun 06, 2003	Jul	CAHN
>A>	BX			0.2MG	N21137 011	Jun 06, 2003	Jul	CAHN
>A>	BX			0.3MG	N21137 012	Jun 06, 2003	Jul	CAHN
>D>	BX		VINTAGE PHARMS	0.025MG	N21137 001	Jun 06, 2003	Jul	CAHN
>D>	BX			0.05MG	N21137 002	Jun 06, 2003	Jul	CAHN
>D>	BX			0.075MG	N21137 003	Jun 06, 2003	Jul	CAHN
>D>	BX			0.088MG	N21137 004	Jun 06, 2003	Jul	CAHN
>D>	BX			0.1MG	N21137 005	Jun 06, 2003	Jul	CAHN
>D>	BX			0.112MG	N21137 006	Jun 06, 2003	Jul	CAHN

*SEE PREFACE SECTION 1.4 LEVOTHRYROXINE SODIUM

H



APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

25th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2005

LANSOPRAZOLE; NAPROXEN

CAPSULE, DELAYED REL PELLETS, TABLET; ORAL
NAPRAPAC 250 (COPACKAGED)
TAP PHARM 15MG;250MG N21507 002 Nov 14, 2003
NAPRAPAC 375 (COPACKAGED)
TAP PHARM 15MG;375MG N21507 003 Nov 14, 2003
NAPRAPAC 500 (COPACKAGED)
+ TAP PHARM 15MG;500MG N21507 004 Nov 14, 2003

LANTHANUM CARBONATE

TABLET, CHEWABLE; ORAL
FOSRENOL
SHIRE PHARM 250MG N21468 001 Oct 26, 2004
+ 500MG N21468 002 Oct 26, 2004

LATANOPROST

SOLUTION/DROPS; OPHTHALMIC
XALATAN
+ PHARMACIA AND UPJOHN 0.005% N20597 001 Jun 05, 1996

LEFLUNOMIDE

TABLET; ORAL
ARAVA
AVENTIS PHARMS 10MG N20905 001 Sep 10, 1998
+ 20MG N20905 002 Sep 10, 1998
+ 100MG N20905 003 Sep 10, 1998

LEPIRUDIN

INJECTABLE; INJECTION
REFLUDAN
+ BERLEX 50MG/VIAL N20807 001 Mar 06, 1998

LETROZOLE

TABLET; ORAL
FEMARA
+ NOVARTIS 2.5MG N20726 001 Jul 25, 1997

LEUCOVORIN CALCIUM

INJECTABLE; INJECTION
LEUCOVORIN CALCIUM

AP		BEDFORD	EQ 50MG BASE/VIAL	N89384	001	Sep 14, 1987
AP			EQ 100MG BASE/VIAL	N89717	001	Mar 28, 1988
AP	+	MAYNE PHARMA USA	EQ 50MG BASE/VIAL	N08107	002	
AP	+		EQ 100MG BASE/VIAL	N08107	004	May 23, 1988
AP	+		EQ 350MG BASE/VIAL	N08107	005	Apr 05, 1989
AP		PHARMACHEMIE	EQ 350MG BASE/VIAL	N40262	001	Dec 15, 1999
AP		PHARMACHEMIE USA	EQ 50MG BASE/VIAL	N89628	001	Apr 17, 1997
AP		SICOR PHARMS	EQ 50MG BASE/VIAL	N81278	001	Sep 28, 1993
AP			EQ 100MG BASE/VIAL	N81277	001	Sep 28, 1993
AP			EQ 350MG BASE/VIAL	N40174	001	Jun 12, 1997

LEUCOVORIN CALCIUM PRESERVATIVE FREE

AP		BEDFORD	EQ 10MG BASE/ML	N40347	001	Apr 25, 2000
AP	+		EQ 200MG BASE/VIAL	N40056	001	May 23, 1995
AP			EQ 350MG BASE/VIAL	N40335	001	Apr 20, 2000
AP		BIGMAR BIOREN PHARMS	EQ 200MG BASE/VIAL	N40258	001	Feb 26, 1999
	+		EQ 500MG BASE/VIAL	N40286	001	Feb 26, 1999
AP	+	HOSPIRA	EQ 10MG BASE/ML	N40147	001	Jun 25, 1997
AP		LUITPOLD	EQ 50MG BASE/VIAL	N40338	001	Jan 31, 2001
AP		SICOR PHARMS	EQ 10MG BASE/ML	N40332	001	Jun 28, 1999